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A SYSTEM OF SYPHILIS

VOL. III

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A

SYSTEM OF SYPHILIS

IN FIVE VOLUMES

EDITED BY

D'ARCY POWER, M.B. OXON., F.R.C.S.

AND

J. KEOGH MURPHY, M.C. CANTAB., F.R.C.S.

WITH AN INTRODUCTION

BY

THE LATE SIR JONATHAN HUTCHINSON, F.R.S.

VOL. III

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VISCERAL SYPHILIS

BY

WILLIAM OSLER, M.D., F.R.S.

AND

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VISCERAL SYPHILIS

CHAPTER I

FEVER

Syphilitic Fever. Being an infectious disease, syphilis frequently gives rise to elevation of temperature. In modern times fever is perhaps a less striking symptom, but at the end of the fifteenth and during the early part of the sixteenth centuries, when syphilis assumed epidemic proportions, its diffusion was so rapid and widespread that it was called the great pox, or *the pox* (*variola magna*), as compared with small-pox, owing probably to the intensity and persistence of the cutaneous features. By many of the writers of this period fever was especially referred to. A graphic description of it is given in the personal record of Ulrich von Hutten in his 'de Guaiaci' (1519).

The earlier investigations were made in the absence of the thermometer, and hence lack accuracy. John Hunter says (1786): 'This fever has much the appearance of rheumatic fever and after a time partakes a good deal of the nature of the hectic.' Guntz (1863), a pupil of Wunderlich, was one of the first to study syphilitic fever by accurate methods. Since then important work has been done in England by Bristowe, S. Phillips, and Parkes-Weber in England; by Musser, Janeway, Fitcher, and Birt in America; and by Bäumlér and F. Klemperer in Germany.

Throughout its course the disease may be afebrile even when the most extensive lesions exist, but a large majority of patients have a slight elevation of temperature in the period of incubation. As pointed out by d'Amato¹ visceral disease does not necessarily accompany elevations of temperature. The fever may persist with intermissions for as long as ten years. It occurs at three

periods—preliminary, stage of invasion, and at any time during the tertiary lesions. The relation of fever to the use of mercury in syphilitic patients is not one on which at present much light can be thrown. Undoubtedly some syphilitics show a febrile reaction after the first exhibition of the drug. The question has recently been discussed by Lindenheim,² who believes that a certain number of these cases may be due to a complication or to an independent fever-producing condition, while others may be due to an accentuation of the secondary symptoms by the drug, or perhaps to ulceration of the throat, stomatitis, enteritis, &c., rather than from poisoning by the drug itself.

I. *Preliminary Fever.* With the weakness, loss of appetite, and pallor which accompany the period of incubation there may be no fever, but in some cases it may be present. A rigor may be the first sign, and may be followed by headache, nausea, and pain in the limbs.

II. *Fever of Invasion.* Usually when the patient is first seen there is no fever. Statistics on this point give 25–35 per cent. as the proportion with fever. It is probable, however, that if cases could be examined at frequent intervals during the day some fever would be found in a larger proportion. The fever may occur one week or two weeks before the eruption appears. According to Fournier, it may be intermittent, remittent, continuous, or irregular, and is accompanied by other signs, namely headache, malaise, and a dirty tongue. Where malaria occurs it is liable to be confounded with the aestivo-autumnal type of that disease.

The intermittent form of fever is less frequent. There are pains in the limbs and about the joints which, with slight fever, may lead to the diagnosis of acute rheumatism. A remarkable case of this kind was seen in a young woman of good family who had had pains in the joints and slight fever, and had been confined to bed for three or four weeks. She had an irregular heart, on which account one of the writers was consulted. The case eventually proved to be secondary syphilis following a chancre on the lip. In another case—a young student—fever with the unusual complication of parotitis occurred during the stage of eruption. In this stage the fever may simulate

typhoid, and has been referred to by Fournier as 'Typhose syphilitique'.

III. *Fever of the Tertiary Lesions.* It is to be regretted that more attention is not paid in the diagnosis of obscure fevers to the fact that tertiary syphilis may give rise to fever of long duration simulating almost every type. This fact should be borne in mind in the diagnosis of these cases. A deep-seated tertiary lesion may be entirely without symptoms, and fever does not invariably accompany even an extensive lesion. It is not possible as yet to say why fever is present in some cases but not in others. When the liver is affected, it has been attributed to a deficiency of the filtration mechanism between the portal and systemic blood systems. Mannaberg³ has recently called attention to the frequency with which syphilitic fever is associated with lesions of the liver. The toxins produced by the spirochaete may in some instances stimulate a febrile reaction of the tissues. It is possible also that the thermogenic centres in the brain may be affected; and, lastly, in some rare cases gummata become secondarily infected with pyogenic organisms. The diseases for which this kind of fever is most apt to be mistaken are:—

(a) Rheumatic Fever. Nodes growing close to joints may cause periarticular enlargement with pain, and if fever is present at the same time the case may be regarded as one of acute rheumatism. This was so in a girl of 19 years seen by one of us; the elbows, one wrist, and both knees were affected. There was slight elevation of temperature, and a day or two elapsed before the true nature of the case was recognized. The correct diagnosis was suggested by finding nodes on the clavicles and after a more careful examination of the joints.

(b) Malaria. The case reported by Sidney Phillips is a typical instance of syphilitic fever being mistaken for ague, even though there was no history of the patient having been abroad or having resided in a malarial district. The accompanying chart (Plate I) from that case will show the similarity of the oscillations of temperature in the two diseases. Another case seen by one of us has been fully reported by Fitcher; a physician, aged 59, had chills and fever which he himself regarded as malarial, but

the fever resisted all treatment with quinine. The diagnosis in this case was made on seeing him stripped; he had a rupial eruption and tender nodes on the shoulders and sternum.

(c) Typhoid Fever. Cases which are mistaken for typhoid fever are rare. Of 3,076 cases admitted to the London fever hospitals wrongly certified as having typhoid fever only ten were subsequently found to have syphilis. The following case reported by Fitcher is a typical example. The patient, aged 39 years, had irregular fever for three weeks previous to admission. The temperature chart showed an intermittent and remittent fever from August 8 until September 16. He had a furred tongue. There were no malarial parasites in his blood. The spleen was enlarged. A continuous fever of this type in the autumn which resisted quinine was naturally regarded as typhoid. It was not until September 12 that suspicion was aroused and W. S. Thayer noticed the presence of thickening of the clavicles from old nodes. There was a definite scar on the glans penis, and the patient acknowledged infection. Potassium iodide was given, and by September 16 the temperature was normal. No further rise of temperature took place, and he was discharged on October 3 perfectly well. J. D. Rolleston⁴ has fully reported two cases of syphilis which simulated typhoid fever.

(d) Tuberculosis. The simulation of pulmonary tuberculosis by syphilitic fever is most important. Many writers have referred to it. Janeway reported a series to the American Association of Physicians in 1898. In a recent monograph Sargent⁵ discusses the relation of the two diseases. It is in the form in which there are sweats, irregular hectic fever, and loss of weight associated with slight cough, that tuberculosis is suspected. The absence of well-marked physical signs and of bacilli in the sputum should suffice to make the physician on his guard against too hasty a diagnosis. The liver may be enlarged, irregular, and tender; it is this feature that may suggest the proper treatment, which is usually followed by prompt recovery.

CHAPTER II

SYPHILIS OF THE TRACHEA AND BRONCHI. SYPHILIS OF THE THYROID

Incidence. Of 112 cases collected from the literature by Conner the greatest number, 38 per cent., occurred between the ages of 30 and 40, the numbers in each decade increasing up to that age and decreasing beyond. The youngest patient was 14 months, the oldest 73 years. 57 per cent. were males, 43 per cent. females. No special time after the infection could be found as most frequent; the shortest period from the date of infection was 9 months, the longest 42 years. The affection occurs both in the acquired and in the inherited form, and in the latter may appear as late as 20 years. In this series of cases the trachea and bronchi were affected in 32.6 per cent., the upper third of the trachea alone in 19.7 per cent., the lower third of the trachea in 15.3 per cent., while the middle third in only 1.7 per cent. Both bronchi alone were affected in 4.2 per cent.; one bronchus alone in 6.8 per cent.

Morbid Anatomy. In the secondary stage the tracheal and bronchial lesions are rare and unimportant in their consequences. Lancereaux describes areas of hyperaemia or violet-red spots. Mucous patches have been seen in the trachea. The tertiary lesions, on the other hand, are always grave, and are often so extensive, so destructive, or so closely related to such important organs, as to threaten life. Syphilis affecting the air-passages has a special predilection for the region of bifurcation of the trachea, but it is met with in the upper or middle third and may be confined to one bronchus or to the branches of one bronchus. Most cases have been found to present tracheo-bronchial syphilis as well as other tertiary lesions, but Orth has described this as the only tertiary lesion. Following Conner,⁶ the lesions may be grouped as

follows :—(1) Gummatous swellings, circumscribed and diffused ; (2) Ulcers, single or multiple ; (3) Distinct scars or diffuse thickening of the endotracheal connective tissue, the result of gummatous infiltration ; and (4) Fibrous peritracheitis and bronchitis.

1. *Gummata* may be seen during life or after death ; they appear as rounded red tumour masses projecting into the lumen, sometimes almost filling it ; they may be single or multiple. Some gummata may affect a large area of the trachea, showing fibrinous or purulent infiltration of the surface, which is raised above that of the rest of the trachea.

2. *Ulcers* may be single or multiple, as their origin from gummata would imply ; some are at least 1 inch in diameter. Their bases may be formed of the submucous or cartilaginous layer, and they may show necrosis and sloughs. Portions of the cartilages may be detached, perforation of the whole thickness of the trachea may ensue. Thus perforation of the right branch of the pulmonary artery, of a bronchial artery, of the aorta, and of the superior vena cava have been described, and perforation of the oesophagus and of a lung vessel ; peritracheal or mediastinal abscesses have resulted from such accidents.

3. *Endotracheal fibrous tissue*. Isolated scars may be small or with radiating bands of connective tissue ; or transverse bands partially or completely encircling it may so markedly constrict the lumen as only to admit a goosequill. The cicatricial tissues, on the other hand, may extend further and deeper, involving the cartilages in its meshes and extending superficially for 2 inches or more in the length of the tube. An extensive peritracheitis may coexist.

4. *Peritracheitis*. This may be combined with endotracheitis or not. It is usually seen about the lower end of the trachea and bifurcation, which may be encased in a dense mass of connective tissue. The lymph-glands in connexion with the tracheo-bronchial system are usually enlarged. An extension of the process from these nodes may affect the recurrent nerves, which are frequently paralysed either partially or completely.

Of associated lesions the following are the most important : The *larynx* is very frequently affected. Vierling gives 63 per cent.

as the proportion, but this is much in excess of Conner's estimate, which is 12 per cent. It is most common when the condition is severe and the lesions extensive. In the *mouth, nose, and throat*, old or recent syphilitic affections may be found in a large proportion of cases. In the lungs changes are found in 10 per cent. (Conner), sometimes interstitial pneumonia, occasionally distinct gummata.

Symptoms. The earliest as well as the most persistent symptom is cough, the result of an irritative lesion in the respiratory path. It is unimportant in a small minority of cases. It may be dry, with expectoration, or paroxysmal: in rare cases it resembles that of thoracic aneurysm. The sputum, owing to the variety of lesions which may be at the root of the trouble, may be bloodstained, mucoid, purulent, or nummular; it may also be fetid. Fragments of tracheal or bronchial cartilages may occur in the expectoration. In a small proportion haemorrhage occurs; it may be so profuse as to cause death, or, on the other hand, may be nothing more than a slight tingeing of the sputum.

Dyspnoea is the most constant as well as the most distressing of all symptoms. It may be absent at rest, and only come on during exertion. A second form frequently associated with the first is paroxysmal, and is seen as attacks of orthopnoea, air hunger, cyanosis, stridor, inspiratory retraction of the tissues at the base of the neck, feeble pulse, and sometimes unconsciousness. The attacks may occur in cases not otherwise subject to dyspnoea, or they may be brought on by exertion, by eating, or at night. The attacks may be so severe as to cause death. The cause of such attacks is probably to be sought in obstruction to air entry into the lung, the increased respiratory effort causing obstruction to the pulmonary circulation, this being followed by a failure of the heart. The type of breathing when the pulmonary circulation becomes embarrassed may be either slow and deep or rapid and shallow. Stridor is present in a large number of cases. It is more frequently of the inspiratory type, but may also be expiratory or both. In some degree its type depends on the site of the constricting lesion—a bronchial lesion may give rise to dyspnoea exactly like that in emphysema.

Pain is sometimes present (17 per cent. in Conner's series); it may be located behind the sternum or in the region of the larynx; the site of the pain is no guide to the position of the lesion. *Tenderness* may be present over the trachea. The voice may be altered; it may be weak, or *aphonia* may be present. In cases with obstruction to air entry, indrawing of the tissues at the root of the neck may be seen. Gerhardt has put forward the view that in this condition there is limitation of the laryngeal excursion in respiration as compared with laryngeal obstruction. The signs in the lungs are very varied; in some the tracheal stridor is so great as entirely to obscure any auscultatory signs in the lungs, in others the signs have been those of bronchitis or of chronic phthisis.

Of rarer physical signs there may be mentioned, dysphagia, emaciation, night sweats, *pulsus paradoxus*, *tracheocele*.

Diagnosis. In the early stages, or if the cicatricial tissue has not been sufficient to give stenosis, there may be no obstruction to respiration. Under these circumstances the diagnosis will rest chiefly on the absence of tubercle bacilli from the sputum, possibly of bronchial or tracheal elements, and also upon the presence of any lesion which can be viewed by tracheoscopy or bronchoscopy.

Cases with stenosis, however, comprise the largest number. In the condition of obstruction to air entry or exit there exists usually dyspnoeic breathing, either prolonged or laboured, a stridulous sound chiefly if not altogether inspiratory, and a sinking in of the tissues at the root of the neck and in the epigastrium. Laryngeal obstruction can usually be eliminated by direct examination. A careful inspection and palpation of the throat will exclude local conditions, such as retropharyngeal abscess; while examination of the trachea as far as it is accessible to palpation from without will often reveal a thickening in the affected region. Gerhardt has made the proposition that in laryngeal obstruction there is a considerable downward movement of the larynx during inspiration which is absent in tracheo-bronchial obstruction. The point at which the stridor is heard loudest by auscultation is usually nearest the site of the obstruction, but this is not so if the constriction is behind the sternum; in this case the stridor may best

be heard over the larynx. The normal breath-sounds heard over the trachea may be absent. A careful comparison of the signs on the two sides of the chest will usually reveal a one-sided bronchial stenosis. A lesion involving the trachea or bronchi having been established, it is necessary to exclude other causes of the lesion, such as foreign bodies, by the history of the ailment and, if possible, by direct observation. Other granulomata, such as tuberculosis, glanders, &c., must be excluded by the means usually adopted in differentiating between these infections.

Prognosis. As will readily be imagined, the disease is serious, the mortality amongst Conner's 128 cases being at the rate of 76 per cent. Death is produced by pneumonia, suffocative attacks, sudden profuse haemorrhage, or gradual exhaustion and cardiac failure. The earlier the diagnosis the less grave is the prognosis, and hence, when the lesions are accessible and readily recognized, the outlook is better. The acute lesions being more readily controlled by antisyphilitic treatment are less severe than those which are the result of slowly progressive sclerosis. The condition of the heart and lungs in an affection in which such stress is placed upon them must necessarily affect the outlook.

Treatment. Antisyphilitic treatment in all but a few cases has caused a marked improvement. The nature of the lesion could not be exactly determined in all. It is probable, therefore, that some improvement ensues even in the more chronic forms of the disease. Potassium or sodium iodide in large doses is the drug from which most benefit is likely to be derived. Care should be taken not to push the drug too quickly, for sudden oedema of the mucous membrane has been described as a result of this treatment. Some relief, if not considerable improvement, may be expected in the mechanical disabilities of stenosis by dilatation of the stenosed tube either from above or through a tracheotomy tube. The presence of the stricture in a bronchus need be no bar to this method in skilled hands.

Tracheotomy may be necessary either for the relief of urgent symptoms of dyspnoea or for mechanical treatment by bougies. Even when the stricture is some distance below the tracheotomy wound the passage of a long tube may be effectual in relieving

symptoms, and therefore offers a means of more permanent benefit.

Bronchiectasis. Included in this term are all cavity formations in the lungs consequent upon syphilis of the bronchi. It is not rare in association with syphilis of the lungs, resulting either from breaking down of lung substance about the bronchi or from bronchial constriction and dilatation.

Morbid Anatomy. In one type the lower lobes are the seat of an interstitial pneumonia, associated with which is a general dilatation of the bronchi of the part. The whole of the lobe is usually affected; the pleura is adherent and is considerably thickened. The lobe is large and firm. On section there are bronchiectatic cavities separated by a greyish fleshy tissue without that firmness usually seen in interstitial tissue. The cavities are rounded or elongated, and may contain clear liquid, caseous, purulent, or putrid matter. In another form there is a large single cavity often in the upper lobe with loss of substance as large as a hen's egg. Its walls may be smooth and formed of a thickish membrane. The cavity may contain mucus or caseous matter. The rest of the lung may show no change, or perhaps a few areas of cicatricial tissue. A third type is that which follows on constriction of one of the main or lesser bronchi.

Symptoms and Physical Signs. The symptoms which the different forms of the disease give do not correspond always to a definite anatomical picture. Of general signs *fever* is the most common, though it may be absent in some cases, especially in the earlier stages, and, as in other forms of bronchiectasis, it seems to depend not so much on the condition itself as upon the presence of a superadded infection. Thus a normal temperature is more frequently seen in the case of an isolated non-suppurating cavity and in those cases in which the lower lobes are cystic and filled with mucous contents. *Wasting and loss of strength* accompany grave lesions, and are, as in tuberculosis, a measure of the degree to which the infection has laid hold of the subject. At the same time the skin often assumes a pallor with an earthy tint which is peculiar to the syphilitic infection.

The cough does not present any special feature, but it is

often more severe in the morning. The *expectoration* is at first muco-purulent, and in cases in which signs are not marked the diagnosis of chronic bronchitis is often made. Sooner or later, when the bronchiectatic condition is well established, the sputum becomes very abundant, purulent, and with a foetid odour. It is most abundant in the morning when the patient begins to move about, and on standing it settles into layers. In cases when the formation of cavities is the result of the breaking down of gummatous masses, the sputum consists of small masses of a greyish-white or reddish substance, with more or less fluid of varying consistence.

Haemoptysis is occasionally observed, and may be so abundant as to cause death. Pain is rare ; tenderness on pressure may be present. Dyspnoea may be very marked out of proportion to the physical signs and accompanied by some degree of cyanosis. It is probable that firm pleural adhesions may in some cases be the explanation of this sign.

The physical signs, not different from those of bronchiectasis from other causes, consist chiefly of dullness, the signs of a cavity, &c., &c. Clubbing of the fingers may be present.

Diagnosis. Clinically the disease shows itself under certain forms, of which the following may be mentioned :—

1. *Larval form.* These are the cases with the signs of chronic bronchitis associated with small dilatations, the result of sclero-gummatous lesions. Careful inquiry and observation may show that the expectoration is different from that in chronic bronchitis in being more abundant or foetid, and auscultation may detect few of the sibilant rhonchi and moist râles which are so characteristic of that condition. Repeated examination should settle the diagnosis ; there may be a slight alteration in the resonance of the middle region of the lung behind ; slight bronchial breathing may be present at one time and disappear at another. Radioscopy may give considerable help under such circumstances.

2. *Bronchiectatic form.* In this the signs are those of the ordinary forms of bronchiectasis, with the affection chiefly in the lower lobes of one or both lungs.

3. *Pseudo-tuberculous form.* This is the form mistaken for

pulmonary tuberculosis owing to the presence of one or more definite cavities in the neighbourhood of the upper or lower apex. The general signs are well marked. The symptoms, such as wasting, night sweats, haemoptysis, may be the same in both, and the physical signs offer little means of distinction. In the syphilitic disease the affection is unilateral, whilst in tuberculosis at such a stage it is nearly always bilateral, and, further, the signs are more basal than in tuberculosis. The sputum at such a stage would not be likely to show tubercle bacilli. Any of the three forms may terminate by becoming gangrenous.

Syphilis of the Thyroid Gland. Engel Reimers records that half the cases of early syphilitic infection show some swelling of the thyroid. No anatomical observations have yet been made, and it is supposed that the swelling is due to an increase in the blood content of the organ and possibly to oedema. The greater number of recorded cases of syphilis of the thyroid have been gummata. Five cases have been reported in new-born babes or children; six cases have been recorded in adults.⁷ The symptoms have been a goitrous swelling and occasionally myxoedema. Simmonds has recorded a case of diffuse fibrous thyroiditis in a female of 67, the result of syphilis. The gland was small, firm, and largely fibrous on cross section. Microscopically there was a laminated arrangement of connective tissue with here and there collections of round cells. In the neighbourhood were many new vessels. There was destruction of the acini. The condition did not give rise to myxoedema.⁸

CHAPTER III

PULMONARY SYPHILIS

Incidence. Until more certain means are applied it is impossible to estimate with any degree of accuracy the frequency of pulmonary syphilis, particularly in the tertiary stage. On one point there is agreement—physicians as well as morbid anatomists acknowledge the extreme rarity of the disease. Thus J. K. Fowler,⁹ in a study which included all the London museums, was only able to point to twelve specimens, and two of these were of a doubtful nature. Of 2,500 autopsies at Johns Hopkins Hospital, lesions which were believed to be syphilitic were present in twelve cases. In 6,000 cases of syphilis taken from the records at the Hospital at Copenhagen¹⁰ pulmonary syphilis was noted only in two; and in eighteen autopsies on subjects who had acquired syphilis, lung lesions were found three times. Petersen in eighty-eight autopsies of acquired syphilis found lesions in eleven. It is probable that in clinical investigations many cases either escape recognition or are never treated, while in post-mortem records the particular ideas of the investigator as to what constitutes a syphilitic lesion are to be taken into account. The difficulty in reaching the conclusion as to the nature of a case may be gathered from the fact that of Hiller's eighty-four collected cases with autopsies, Councilman regarded only twenty-eight as shown to be definitely syphilitic.

MORBID ANATOMY

Hereditary Syphilis. *White Pneumonia* is found in the lungs of premature infants or those who have survived only a short time. The condition was first described by Virchow. The general appearance of the child is cachectic, and may have external

lesions denoting congenital syphilis. The lungs are either airless or very much deficient in floating power, they are increased in size, and those parts which are solid show in their external parts the markings of the ribs. The change may affect both lungs everywhere, or may be limited to one lung or to a lobe. On section it is whitish, greyish, or marbled grey and red ; it contains little or no air on squeezing. The granular appearance of the lung consolidated from lobar pneumonia is absent, the cut surface is smooth or may present an appearance like the pancreas—pancreatization. The other organs, liver, spleen, peritoneum, may show lesions of congenital syphilis. Microscopically the interstitial tissue is not increased, though the alveolar walls are thickened and the alveoli as well as the smaller bronchi are filled with cells, some epithelial, some inflammatory, many of which are breaking down and undergoing fatty degeneration. The alveoli are large, there is little blood in the capillaries. Ecchymoses may be present, especially under the pleura. The bronchial glands are large and fleshy. This, however, is not the only type : one form is called adenomatous and consists of alveoli lined by cubical epithelium and containing a few free cells, the rest of the substance of the lung being made up of a fibrous stroma infiltrated with cells from the cubical epithelium of the alveoli. Stained by Levaditi's silver method, large numbers of spirochaetes are everywhere seen. The vessels often show marked periarteritis (Plate II).

Interstitial Pneumonia is present in still-born infants or those who have survived birth but a few days. It is a more advanced stage of the previous form. The lungs are large, hard, and of a pale or dark-grey colour. As in the previous form, both lungs may be affected, a single lobe or a portion of a lobe. On section the lung has a coarse appearance due on minute inspection to an increase in the interlobular connective tissue, which forms broad meshes. The lung contains air and feels harder and tougher than normal. Even more frequently than in the previous form there may be syphilitic changes in other organs.

Microscopically there is a small round-cell infiltration of the interalveolar connective tissue, and by appropriate means a

general or patchy increase in interstitial tissue can be demonstrated. There is an increase of it about the small bronchi. In some parts there is a great increase in the number of small vessels in the septa, many of which are tortuous. The arteries occasionally show typical syphilitic arteritis. The alveolar epithelium may be unaffected or shows degenerative changes (fatty), or may contain pigment granules; in parts where there is much interstitial reaction the cells may be more columnar.

White Broncho-pneumonia. An extremely rare form, having all the appearances of a broncho-pneumonia due to other agents, though sufficiently characteristic in its whitish or greyish-white appearance to be distinguished by the naked eye. The change is primarily in the small bronchi, the alveoli being affected secondarily.

Gummata are rare, but differ in no particulars from those found in the acquired disease to be described.

Acquired Syphilis. *Gummata*, singly or in numbers, and varying from the size of a pin-head to that of a hen's egg, are situated either in relation to one of the larger fibrous septa of the lung, especially near the root, or less often in the neighbourhood of the pleura, and still more rarely at the apex. The first stage is probably to be seen in the minute patches of caseous necrosis in the neighbourhood of a vessel affected by endo-, meso-, or peri-arteritis; these patches may be seen in the neighbourhood of larger gummata. The caseous degeneration gives rise to the formation of a connective-tissue capsule which is more or less in evidence according to the age of the lesion: if the caseous process increases, the size of the gumma increases also, until there is a yellowish-white mass surrounded by fibrous tissue merging gradually into the parenchyma of the lung. This yellowish mass may be of the consistence of bone marrow or, if the process has been slower, it may be of a cartilaginous hardness and somewhat translucent. In the later stages there is an extremely thick capsule of fibrous tissue surrounding a yellowish mass—the remains of the caseous matter. Pneumonic processes may be present near the older gummata; in the neighbourhood of the more active lesions fibrous tissue in radiating strands pierces the

neighbouring tissue. Gummata of the lung generally become fibrosed ; more rarely they soften and ulcerate into a bronchus.

Nodules of fibrous tissue in the lungs have been described as gummatous cicatrices, but their distinction from similar lesions due to tuberculosis is so uncertain that, as the matter stands at present, it is wise to leave them out of account.

Microscopically the pulmonary gumma differs little from this structure in other organs. In the necrotic portion there may be a trace of alveolar structure, and it is often possible in the centre of the necrotic mass to distinguish a larger vessel. As in other gummata, the fibrous tissue gradually disappears when traced away from the centre, often being associated with an infiltration of the tissue with round cells which here and there may be grouped in masses suggesting the formation of accessory gummata. At the periphery there is an active proliferation within the alveoli of a cubical epithelium, an appearance which has been taken as typically syphilitic in character ; but as it is found in the neighbourhood of old tuberculous lesions it has no particular significance. Giant cells are not usually found, and never of the same type as those in tuberculosis ; when present they are large cells with several nuclei. Spirochaetes, so far as we know, have not been demonstrated in gummatous lesions.

In general it may be said that pulmonary gummata present no special feature which may serve as a diagnostic sign ; all features must be taken into account, and the more skilled in morbid anatomy the observer the less often are mistakes likely to be made. The following are the most characteristic points : their seat is at the base or hilum, the number is limited, their volume and density are different ; there are none or only a few giant cells, miliary gummata are present in the surrounding fibrous tissue, and there are marked alterations in the vessels. Other forms of pulmonary syphilis allied to gummata, e.g. a massive caseating pneumonia or a broncho-pneumonia, are described by some authors, and some cases have been reported which may be of that nature, but their syphilitic etiology is extremely uncertain as yet.¹¹

Sclerosis may present itself either as a local or general process ;

in the former case it probably results from a gumma which has been absorbed. The sclerotic tissue, especially in the localised forms, is hard, creaks under the knife, is of a whitish-grey tint, but if much anthracosis is present, it is greyish black or black. The parts affected are retracted. Radiating lines of connective tissue stretch outwards into the surrounding tissue. Sclerosis may be present in subpleural blocks over which there is a retraction of the serous layer. In other cases, especially in very young children, a portion of a lung or even a whole lung may be generally fibrosed, 'carnified,' dense, and sinking in water; giving no crepitus, but rather an elastic sensation as found normally in the pancreas. If the sclerotic process has affected more especially the hilum of the lung it is chiefly found around the large bronchial trunks, and has given rise to the term fibrous syphilitic peribronchitis, but in this case it is usually associated with a syphilitic bronchitis. In extreme cases of localised contraction the organ may have a similar appearance to the botryoid liver. Hermann Weber¹² described and figured the lungs from an undoubted case of syphilis; both organs were fibrosed, especially around the lymphatics and the smaller bronchial tubes; but the chief feature was a dilatation of the lymphatics, which appeared as a network of vessels on the pleural surface filled with a thickish yellow fluid: in a cross section they appeared as opaque whitish spots, not unlike miliary tubercles on first sight, but on closer inspection they could be seen to be the cross sections of dilated capillary lymphatics. The bronchial glands were much enlarged, some being as large as a pigeon's egg, their cross section being marbled red and whitish, the redder parts being very vascular.¹³

Microscopically the fibrous tissue and the fibrotic process do not differ from those due to other causes. Remains of the alveoli are present in the neighbourhood of the sclerotic tissue either as cavities lined by cubical epithelium or as cells arranged singly or in groups.

Syphilitic Phthisis, a mixed form, may consist of fibrous-tissue formation, gummatous changes, and pneumonic affections, as well as cavitation and bronchiectasis. Most examples recall the tuberculous process in everything except that syphilis tends to

affect the tissues around the bronchi ; the condition is well figured in Fowler and Godlee's book.¹⁴

CLINICAL MANIFESTATIONS

Hereditary Syphilis

In the New-born. The symptoms are those of congenital syphilis, and those referable to the lungs are either absent or insignificant compared with those of the skin, liver, spleen, &c. There may be a deficient resonance in some part of the chest. Cyanosis and dyspnoea may be present, and may gradually increase till the patient dies. It is doubtful whether, even under antisypilitic treatment, such children ever live beyond the age of 2 or 3 months.

In Children the cases that have been recorded do not permit of a definite symptomatology in the present state of our knowledge. One case is reported by Fournier of gummata of the lung in a child of 7 who died from an acute illness but without symptoms referable to the lungs.

Acquired Syphilis—Clinical Manifestations

Under present conditions our knowledge of the morbid anatomy of syphilis of the lungs is in advance of that of the clinical features. The following are some of the groups which may be described :—

I. *The Latent Form.* Gummata may be present in the lungs of a patient and yet give no sign or symptom of their presence, even though they are neither solitary nor small. The patient may be well nourished, may suffer from nothing more than a slight cough. Even careful examination of the chest may detect nothing but such a small impairment of resonance or such slight signs in the smaller tubes or parenchyma, that their significance is passed over, especially if the patient has other and more urgent symptoms. These constitute a proportion of the cases which are accidentally discovered to have gummata at the post-mortem examination, the patient having died from some other disease. From the accounts of cases which have

been reported it would appear to be wise to view with considerable suspicion trivial lung signs in a patient with other definite lesions of syphilis.

II. *The Ulcerating Gumma.* Upon theoretical grounds this should give rise to a well-defined group of symptoms, and yet it is possible that some of the cases recorded have been tuberculous. A case is reported by Cube (quoted by Bériel): a man, having had syphilis nine years before, suffered from what was supposed to be tuberculosis of the lung and larynx for two years, gradually becoming worse. He had fever, wasting sweats, and an ill-smelling, abundant expectoration in which occasional bits of 'flesh' would be seen. At the angle of the right scapula he had a patch of dullness the size of the palm of the hand, and definitely limited; medium râles were heard over this area. The apices were free. The amount of the expectoration varied; the more solid portions examined microscopically did not suggest tuberculosis. On being treated by mercurial inunctions the patient recovered promptly; a later attack of fever and haemoptysis was similarly cured.

III. '*Syphilitic Phthisis.*' The careful investigations of J. K. Fowler leave no doubt that a progressive fibro-caseous disease of the lungs exists which is indistinguishable in its clinical features from pulmonary tuberculosis. In his work three cases are carefully reported, and the descriptions leave no doubt in the mind of the reader that the disease in each case was due to syphilis. Another case is reported by Osler.¹⁵ Fowler⁹ lays down the following postulates which must be fulfilled before a diagnosis of pulmonary syphilis can be made:—

- (i) The cases must be complete, that is, the symptoms observed during life must be considered in connexion with the lesions discovered on post-mortem examination.
- (ii) The evidence of syphilitic infection must be undoubted.
- (iii) Repeated examinations of the sputum must have been made, and tubercle bacilli have been invariably absent, and the absence of tubercle from the lungs as the cause of the lesions must be proved by post-mortem examination.
- (iv) Syphilitic lesions about the nature of which there can be no doubt must be found in other organs.

The cough, dyspnoea, expectoration, frequency of haemoptysis, pain, emaciation, are in no respect different from those seen in pulmonary tuberculosis. Night sweats are present in some of the cases. Even the temperature may simulate pulmonary tuberculosis; it may either be moderately high and continuous or intermittent, but in the earlier stages fever may be absent. Even haemorrhage may complicate the disease and still further simulate pulmonary tuberculosis. Remsen¹⁶ reported the case of a coloured man, aged 27, who was admitted to the Johns Hopkins Hospital with haemoptysis. For more than a year he had had cough and shortness of breath, and he was regarded at the out-patient department as tuberculous. He had weakness and wasting of the left arm. The physical signs at the apex of the left lung were impairment of resonance and numerous râles, and there were signs of extensive disease of the right lower lobe. He died suddenly of haemorrhage from the lungs. The case was regarded as one of pulmonary tuberculosis, although no bacilli were found in the sputum. At the post-mortem examination the apex of the left lung felt firm and there were a few scattered nodules on its surface. On section just below the apex, there was a caseous mass surrounded by scar-like tissue. The right lower lobe was almost entirely solid with caseous masses, separated by strands of connective tissue. In the middle there was a cavity of 3.5 cm. in diameter filled with blood, which opened directly into a bronchus, which had eroded into a branch of the pulmonary artery. No tubercles or tubercle bacilli were found. This case shows the existence of a progressive destructive disease, a true syphilitic phthisis.

Buchanan's¹⁷ case is worthy of special mention as being one in which the lung condition seen by the X-rays was observed to disappear under treatment. The patient was a male, aged 48. In October, 1906, he complained of cough, expectoration, dyspnoea, pyrexia, night sweats, and emaciation. There was no family history of tuberculosis. He had had pleurisy in 1898 and again in 1906, the first on the left, the second on the right side. During 1905 and 1906 he had had repeated attacks of bronchial catarrh.

He improved slightly as the result of a two months' holiday in the Canary Isles, but he gradually lost weight on his return, and suffered from constant cough but not much expectoration. There was no haemoptysis, and repeated examination for tubercle bacilli was negative. There was a history of his having contracted syphilis five years before and of having had two years' treatment. When first seen by Dr. Buchanan he was pale, cachectic, with a pulse of 96 and temperature of 101° , and clubbed fingers. There were scars over the left tibia. In October, 1906, he developed a small gumma of the forehead. There was no other evidence of visceral lesions. There was diminished expansion at both lung bases, especially the right. There were no definite physical signs in front, but harsh breathing was present at the left apex with a few rhonchi and inspiratory crepitations. There was friction at the sides. 'Behind two dull areas were present—one at the left base about 3 inches in diameter, circular in shape. Over this the vocal fremitus and resonance were absent, and a peculiar suction sound followed by râles occurred at the end of inspiration. Around the margin of this area fine inspiratory friction crepitations were present.' 'At the right base an oval area of dullness was present about the size of a hen's egg, and directed downwards and outwards; over this the vocal fremitus and resonance were both increased. Inspiratory crepitations, harsh inspiration, and whispering pectoriloquy were present. Other signs were normal.' The nature of the disease was diagnosed from the absence of bacilli from the sputum, the history of syphilis, the presence of a gumma of the forehead.

The X-rays showed two definite circumscribed shadows, corresponding to the areas located by the ordinary examination (see Plates III and IV). Other parts of the lungs were mottled. Treatment by potassium iodide caused a rapid improvement in his general condition and a disappearance of the physical signs. He increased sixteen pounds in weight, the temperature became normal, the clubbing of the fingers disappeared, and the cough ceased. The patient was able to continue his employment without discomfort, and he expressed himself at the end of four months as feeling perfectly well.

We are indebted to Dr. Buchanan, of Liverpool, for the following notes on another case under his care :—

Phthisis Syphilitica—Fibroid Lung of Twenty-five Years' Duration.

E. W., aged 38. *History of the complaint* : In March, 1884, she had inflammation in the left lung and was six weeks in bed. In July, 1884, she was in the Children's Hospital, St. Michael's Hill, Bristol, when she was said to have rapid consumption of the left lung. She was two months in hospital, and attended the out-patient department for two years. In 1886 she went to the Consumption Hospital at Manchester, and was under the care of Dr. Moritz. She was an in-patient for three months in 1888, three months in 1892, three months in 1893, and three months in 1897, with attacks of bronchitis ; the dyspnoea became worse, and there was a constant troublesome cough. She attended this hospital as an out-patient until 1902. In this year she was in the Manchester Royal Infirmary under the late Dr. Thomas Harris, with severe haemoptysis for over seven weeks. She attended as an out-patient afterwards. In 1904 she again had haemoptysis and was in the Manchester Royal Infirmary for seven weeks. In January and February of 1905 she was again in the Manchester Royal Infirmary with dyspnoea and bronchitis : from April to June she was at Cheadle, where she had right-sided pneumonia for three months. She remained an out-patient till March, 1905, when she was sent to Dr. Buchanan by the late Dr. Thomas Harris, who stated that tubercle bacilli had never been found in the sputum, and the inoculation of rabbits at many different times had always been negative. Up to the date of writing she has remained under my care as an out-patient, with occasional admissions to the ward. Her condition on first admission is shown in the two diagrams (Plates V and VI), and in the radiograph (Plate VII). The radiograph shows the extreme displacement of the heart-shadow (the apex-beat is at the angle of the scapula). The left lung is shrivelled up. The whole of the clear area on both sides of the middle line is the right lung, hypertrophied and emphysematous. Her condition at the present time is improving, and the peculiar quacking sounds in the left chest, which could be heard three or four yards away at one time, especially after exertion, are less distinct. Among my out-patients she is known as 'the girl with the ducks in her chest'. It is surprising how slight the dyspnoea is. She does not run any temperature or suffer from sweats, and I have never found any tubercle bacilli in the sputum.*

IV. *Fibroid Form.* This in its clinical features is indistinguishable from the same disease due to other causes. It may

* We are informed in a letter from Dr. Buchanan that the *Spirochaete pallida* was found in this patient's sputum in November, 1906, and that at the time of writing (April, 1909) the patient remains well and the lungs have remained clear.

be entirely latent as regards symptoms attributable to the lungs, and only become manifest when right heart-failure comes on. Such a case is reported by Osler¹⁸ in which the lungs were typically 'pulmolobatus'. Another typical case has been recorded by E. C. Perry.¹⁹

Diagnosis. It has been taught that no diagnosis is complete without having considered the possibility of tuberculosis and of syphilis. As applied to the lesions of the lungs this is a good rule in obscure cases, in which the possibility of syphilis should always be considered. It is well to remember in this connexion the marvellous effect produced by proper syphilitic treatment, as, for instance, in Dieulafoy's patient and one reported by Fowler, both of whom had been pronounced hopeless cases of tuberculosis. Many other such cases are on record. And yet the physician does well to err on the side of a healthy scepticism in regard to lung syphilis; first, because of its extreme rarity, and secondly, because of the harm done to a patient with tuberculous disease of the lungs by being dosed indiscriminately with mercury and potassium iodide.

In a suspected case the history of the patient must be thoroughly investigated for evidence of syphilitic infection, about which there should be no reasonable doubt.

The physical signs afford little if any help in diagnosis, but the suspicion of syphilis should be the stronger if the lesions tend to be basal rather than apical. It has been said that syphilis is apt to attack the middle lobe, but post-mortem records hardly bear this out. The sputum must be frequently examined to exclude tuberculosis, and this is especially necessary when large amounts of breaking-down tissue are being coughed up. The X-rays should not be omitted in doubtful cases as a means of more accurate delimitation of the lesions.

The larynx should be examined by a skilled person, and if possible tracheo-bronchoscopy applied to see if any associated tracheal or bronchial lesion is present, a condition which would strongly suggest syphilis.

It must not be forgotten that syphilis and tuberculosis²⁰ may co-exist, and it does not follow that in a person with

obvious signs of the former the lesions in the lungs are to be attributed to the same cause. Especially is this the case in the congenital form, in which the resistance of the body to the tubercle bacillus has become lowered. Some authors have attributed certain features of the lungs in these subjects to syphilis, certain others to tuberculosis ; but when the anatomical distinctions between tuberculosis and syphilis, apart from the presence of their causative organisms, are uncertain, it is obviously useless to discuss the question from the clinical standpoint.

SYPHILIS OF THE PLEURA

This is seldom seen except as an accompaniment of lung syphilis ; but in the case recorded by Buchanan the patient, before any symptoms pointing to lung disease appeared, suffered from pleurisy on two occasions (Plate VIII). An exudative pleurisy and a gummatous affection have been described. In the cases of chronic lung syphilis the two layers of the pleura become adherent and much thickened.

CHAPTER IV

SYPHILIS OF THE HEART

SYPHILIS of the heart has been mentioned in the literature since the days of Astruc, 1736, and of Morgagni, 1766-7. Later knowledge is due to the work of Corvisart, Laennec, Bertin and Bouillard, and many others.

Morbid Anatomy. Syphilitic changes may affect all three layers of the heart, pericardium, endocardium, and myocardium.

In the *pericardium* the lesion is most often a simple fibrous pericarditis similar to the 'milk-spot' seen so frequently on the visceral pericardium; a percentage of these milk-spots may be syphilitic in origin. The extent of the pericarditis may vary from a very small patch to the greater surface of the pericardium, as in a heart in the possession of one of us in which the whole of the visceral pericardium is thickened and pearly, though not so thick as to prevent the myocardium being visible underneath. Bands connecting the visceral with the parietal pericardium are rare. A gummatous affection of the pericardium is also rare; when present it is in the form of small tubercles scattered here and there. Another unusual form is that in which the smaller pericardial vessels have numerous small aneurysms accompanied by much thickening and an adherence between the two layers.

Syphilitic endocarditis, unlike other forms, is only rarely found on the valves: it chiefly affects the endocardium of the left ventricle and septum. Syphilitic affections of the valves are rarely widespread; only one valve at a time is attacked, and of that only one cusp as a rule. It leads to much less serious changes than other forms of endocarditis. Syphilitic endocarditis is seen as a small localised whitish thickening of the endocardium, or a yellowish-white, often extensive, plate-like mass. Healed gummata are often seen as diffuse yellowish-white thickenings of

the endocardium of the ventricle (see Plates IX and X), which on section may be seen to send fibrous processes into the myocardium. Calcification may be seen in old cicatrices. The structure of endocardial lesions varies according as they are in the acute or healed stage; in the former they are cellular, in the latter they consist of fibrous tissue (Plate X). The endocarditis may spread downwards and involve the muscle, in which case there is a weakening of the ventricular wall and possibly the formation of an aneurysm; such aneurysms may burst and give rise to sudden death from haemorrhage into the pericardium. Again, as in other forms of endocarditis, a gummatous infiltration may give rise to an ulceration, thrombus formation, and embolism.

Myocarditis occurs in two forms, between which there are intermediate varieties; they are the fibrous myocarditis and the gummatous myocarditis. In the first there is a round-cell infiltration of the connective tissue accompanying the vessels; the muscle fibres suffer secondarily, partly from pressure of the proliferating connective tissue and partly owing to the narrowing of the vessels from endarteritis obliterans. When the muscle fibres are destroyed they are replaced by fibrous tissue (Plate XI). These areas of gummatous infiltration may be either circumscript or diffuse. They are found chiefly in the left ventricle near the apex. Giant cells are often seen in these areas. A more general form of fibrous myocarditis (Plate XII) follows a more general syphilitic endarteritis of the coronary arteries and the resulting restriction of the capillary field. The consequences of these changes are a weakening of the muscular wall, hypertrophy, and dilatation.

The second form, the gummatous, occurs usually with gummatous infiltration. All muscular portions of the heart may be affected by gummata, but the commoner sites are the ventricular walls and septum. The structure of heart gummata is similar to those elsewhere, but Stockmann²¹ has figured well-marked giant cells not unlike those in tuberculosis, in addition to the ordinary cellular elements of gummata.

The coronary arteries may be affected as part of a gummatous process or separately; the larger branches are not immune. The

form is chiefly endarteritis obliterans, and may be followed by infarcts as large as three-quarters of an inch in diameter. Ehrlich has described endophlebitis as well as endarteritis.

Symptoms. Syphilis of the heart may show itself in many ways, and it is only by indirect evidence that the condition can be attributed to syphilis. The forms of cardiac trouble under which syphilis of the heart shows itself may be grouped as follows :—

(i) Right heart-failure is seen in a fair proportion of cases showing the typical features, oedema of the skin, dyspnoea, orthopnoea, diminished secretion of urine, enlarged liver, and oedema of the lungs. Attacks of cardiac asthma are of frequent occurrence in the reported cases.

(ii) Left heart-failure in some cases shows itself in headache, giddiness, or fainting; in others it leads to a gradual enfeeblement and failure of strength. In a case observed by one of us the clinical signs were first those of a mitral leak, leading in the later stages of the illness to attacks of right heart-failure, in one of which the patient died. At the autopsy there was a gumma of the septum on the left side which had produced first left ventricular dilatation and mitral regurgitation, followed by right ventricular hypertrophy and finally failure (Plate IX).

(iii) A third form is associated with some form of anginoid attacks, probably due to the affection being chiefly myocardial. In this form palpitation, stitch in the side, pain over the heart, abdominal pain, and pain down the arm have been described.

(iv) Cases with the features of Stokes-Adams' disease have recently been recorded. It may be caused by gummatous change involving the top of the septum, as in one of Keith's cases, or by a gummatous endarteritis affecting the branch which supplies His's bundle. Two of the patients at the Johns Hopkins Hospital with this disease were syphilitic, and one case, which has been fully recorded by Erlanger, who had bradycardia and epileptiform seizures for a year or more recovered completely under specific treatment.

(v) A fifth form has been described by Huchard and Fiessinger as the renal form; it begins with slight oedema of the ankles,

there is a high-tension pulse, tachycardia, and the urine contains albumin.

The frequency with which cardiac syphilis terminates the life of the patients by sudden death is remarkable : of six cases reported by W. P. Herringham,²² all but one were brought to hospital either dead or dying. The cause may be a sudden failure of the cerebral circulation, the rupture of the heart at the site of a gumma, or due to embolism.

Diagnosis. It is the more necessary to make an accurate diagnosis of the syphilitic nature of the complaint as these cases are much more amenable to treatment than any other form of cardiac trouble. The presence of one or other form of cardiac failure in a young or middle-aged person in whom there is no history of rheumatic fever should arouse suspicion. The various systems must be carefully examined for evidence of syphilitic change. In the case previously mentioned of gumma of the septum no other organ in the body was affected ; the patient had been a soldier in India, and denied infection but admitted the risk. The diagnosis is easier when symptoms of angina, such as usually affects older persons, come on early in life, or if the heart enlarges relatively quickly, or if aortic insufficiency is present with no previous history.

SYPHILIS OF THE ARTERIES

Syphilis affects the arteries in a patchy manner similar to atheroma in its general distribution, so that in the aorta we see localised areas of degeneration ; in the smaller arteries the whole circumference of the tube suffers as a rule.

Syphilitic Aortitis. In the aorta the most common site is in the arch, less commonly in the descending aorta, where, according to some authors, atheroma is more frequent. Isolated patches, healed or in a more acute stage, may be seen anywhere in the arch, but a frequent site is just above the aortic valves.

The earlier stages of syphilitic aortitis may not be obvious except to very careful scrutiny. The intima may not be affected at all, or only very slightly thickened and rendered slightly transparent ; macroscopically there may be no change in the media.

When the process is more advanced the portion affected assumes a bluer tint owing to the lack of elastic tissue at the spot affected, and if held up to the light it is more transparent. When the process is more extensive there is an appearance of scarring—the surface is irregular, there may be ridges in the length of the aorta, or arranged in a radial manner, and the whole interior portion affected has lost the yellow normal tint, being replaced by a greyish or bluish-grey colour, with perhaps occasional yellowish patches giving it a mottled appearance. Accompanying this process, but not so definitely of a syphilitic nature, is another more of the nature of atheroma; it begins as a localised swelling of the inner layers, including the intima, and later, either near the surface or in the superficial layers of the media, there appears a yellowish caseous or even calcified area flattened in the direction of the circumference of the artery. This may be a true atheroma accompanying the syphilitic process; it varies in its extent in different subjects, but it may be said that the true syphilitic change in the media can usually be detected below these areas. As will be mentioned later, the elastic tissue at the transparent areas is destroyed; consequently, owing to the natural resilience of the aorta being lost, and if the process extends over a large area, the tube must dilate to accommodate the necessary blood at the requisite pressure to supply the needs of the tissues; such vessels are often found generally dilated. An area may be so weakened that the wall gives under the stress of even the normal pressure of the blood, and an aneurysm is formed. According to the depth of the wall which is ruptured, so one finds the various types of aneurysm—dissecting, saccular, &c.

Histologically the process begins as a round-cell infiltration accompanying the *vasa vasorum*, and a swelling and multiplication of the cells forming their walls; in this respect it differs from the changes in the media induced by the repeated injection of adrenalin, in which there is no change in the *vasa vasorum*. The intima is very much thickened and shows very little structure beyond coarse lamination. If a preparation be stained by Weigert's elastic stain it will be seen that the elastic tissue is

destroyed in the region of the affected *vasa vasorum*, and where the walls are thin and transparent there is very little trace of elastic tissue at all, the ends of the fibres ending abruptly (Plate XIII). In relation with these medial changes there is often a fatty degeneration of the intima or upper layers of the media, which stain well with Soudan III.

In other cases there may be actual gummata with necrosis in the substance of the media, where, as in cardiac gummata, there may be many giant cells with a ring of nuclei. Schmorl has been able to detect the *Spirochaete pallida* in cases of syphilitic aortitis. This has been confirmed by J. Homer Wright,²³ one of whose preparations he has kindly allowed us to use (Plate XIV).

The relation of Syphilis to Aneurysm. Morgagni seems to have been aware of the intimate relation between aneurysm and syphilis. The work of Welch in 1876 called attention to the frequency of aneurysm in soldiers, of which he thought at least 50 per cent. of the cases were associated with syphilis. More recent statistics have shown that in from 20 to 80 per cent. of the cases there is a well-marked history of syphilis. It seems that the more carefully the cases are looked into and the more accurately they are studied, the larger will be found to be the percentage with a luetic history. All writers are impressed with the fact that the age incidence of aneurysm and ordinary atheroma is different, for the greater proportion of patients with aneurysm are within the third and fourth decades. The studies of Chiari,²⁴ Benda, and others have shown us that the type of mesaortitis described previously as a syphilitic affection is almost constantly present in cases of aortic aneurysm; and the recent experimental production of aneurysm by the administration of adrenalin shows that the lesion of the media is the principal element in its formation. Both in syphilis and after adrenalin the degeneration is produced in the media; over these places the intima may be perfectly smooth. When an aneurysm is produced the intima splits, blood passes in under pressure, and an aneurysm is produced. The portion of the wall which bears most of the strain of the pressure of the blood, namely the elastic media, being

damaged, gives way during a sudden strain, and the intima is either burst or bulged into the hiatus produced in the media. Such slits in the media, with aneurysms or undergoing healing, have been described by v. Schrötter and Deland. Laubry and Parvu²⁵ have applied Wassermann's reaction to six cases of aneurysm of the aorta. The reaction was positive in four; yet in the two negative cases there were pupillary changes that are usually taken to be syphilitic.

Periarteritis. Syphilis often attacks the adventitia of the arteries without affecting the media or intima; it occurs especially when the supporting tissue of an organ or membrane is attacked, such as the meninges or the tissue of the lung. A special form of this is localised to certain spots usually from 3 to 5 mm. in diameter, but merging into more diffuse forms; this is called periarteritis nodosa. It is doubtful whether this form is to be distinguished from another somewhat similar affection of the arteries, polyarteritis acuta nodosa. Twenty-eight cases of both conditions have been collected by Carnegie Dickson²⁶ and their etiology discussed. There is little doubt that there is a syphilitic disease of this type affecting chiefly the cerebral arteries. In the condition to which the term polyarteritis acuta nodosa is applied the syphilitic origin is less sure, though in five of the nineteen cases collected by Dickson there was a definite history of syphilis and in two others the conclusions of the writer reporting the case were in favour of syphilis. This latter condition is one which affects the arteries of the intestine, heart, liver, peritoneum, and kidneys, and only rarely the brain arteries. There is little histological difference between the two conditions, and all authors are agreed that it is caused by a toxin, probably bacterial. The *Spirochaete pallida* has not been demonstrated in the lesions.

The nodular periarteritis as it occurs in the brain arteries is not localised to any group, but is most frequently found in the vertebrals, the basilar, and the arteries composing the circle of Willis. The nodules are irregularly scattered, and vary usually from the size of a millet-seed to that of a pea. Wilks, in 1863, described them as 'hard round grains' projecting like tubercles.

At the site of the nodules there may be an aneurysmal dilatation of the artery with or without thrombus formation.

There is no sharp line histologically between the various forms of periarteritis. When the condition forms a part of a general syphilitic inflammation of an organ, the adventitia is infiltrated with round cells and fibroblasts, and is of a much looser texture than normal. In the nodular form there is either a localised infiltration of the adventitia with round cells and fibroblasts with commencing caseation, or more definite caseous gummata. The inflammation in more advanced stages may spread inwards and affect the media or adventitia.

Acute Gummatus Arteritis may be seen in many situations in the neighbourhood of gummata provided the process is acute enough ; it consists in an infiltration with inflammatory cells and produces ultimate destruction of the entire thickness of the artery. In the smaller vessels, as seen histologically, it affects the whole circumference of the vessel, but in the larger arteries its extent may be more limited. To this process may be ascribed the acute perforating ulcer of the aorta.

Obliterative Endarteritis is seen most frequently in arteries of small calibre, especially in the neighbourhood of subacute or healing gummata, but it may attack vessels in the absence of gummata. It may be limited to one system of vessels, e.g. the coronaries or the posterior tibials or brain arteries. It consists in a cellular proliferation of the intima leading ultimately to complete obliteration of the lumen (Plates XV and XVI). Thrombosis may hasten this process. The *Spirochaete pallida*, so far, has not been found. This form of endarteritis, though much associated with syphilis, is not specific. It has been described as the result of toxic agents, e.g. tuberculosis, and as a senile change.

The Symptoms of Syphilitic Arteritis can only be mentioned in general. Conditions which affect the aorta give evidence of their presence either as the symptoms of aneurysm in its various sites and stages or, if the affection has led to a general dilatation of the aorta, hypertrophy of the heart with or without a diastolic murmur may be the picture. If the aortitis affects the neighbourhood of the coronary arteries, the condition is

one of angina pectoris such as has been described in cardiac syphilis.

The syphilitic affection of arteries gives rise frequently to haemorrhage ; this is seen in aneurysms, in cerebral haemorrhage, and in pulmonary haemorrhage. Perhaps a more frequent clinical picture is seen in gradual obliteration of the lumen of an important set of vessels, giving rise to intermittent interruption of the blood-supply of the organ with or without thrombosis. In the limbs intermittent claudication is the result. But it is in the brain that these symptoms have been best studied ; there may be transient paralysis of the hemiplegic type finally culminating in a hemiplegia which is permanent, due to thrombosis ; or there may be a succession of monoplegias finally becoming hemiplegia.

CHAPTER V

SYPHILIS OF THE DIGESTIVE SYSTEM

THE SALIVARY GLANDS

SWELLING of the parotid and submaxillary glands have been described in the secondary stage and may suggest ordinary mumps. Tumours of the gland have been considered to be syphilitic. Lancereaux found them sclerosed and small in one case. Even the sublingual gland has been invaded by the syphilitic process. The parotid is the gland most frequently affected. The condition may be so acute that the greater part of the gland is destroyed.

PANCREAS

Incidence. Out of 188 cases of disease of the pancreas syphilitic changes were present in three (L. Oser). Pancreatic lesions are more frequent in the hereditary than in the acquired disease, the organ being affected in 20 per cent. of newborn infants suffering from syphilis.^{27, 28} The liver, spleen, bones, and lungs are frequently affected at the same time as the pancreas, especially the liver.

Morbid Anatomy. In the congenital form the gland is affected with a chronic interstitial inflammation with great destruction of the glandular substance not, as a rule, including the islands of Langerhans. Miliary gummata as in the liver have been described. The vessels show changes of their intima and adventitia. In adults, chronic interstitial pancreatitis is the more frequent form ; but both gummata and cicatrix formation have been met with.

Symptoms. The commoner type of case is that associated with dyspepsia, wasting and fatty stools, the diagnosis being made from the evidence of syphilitic disease of other organs. If the head of the pancreas be affected by a gumma, it may give rise to a picture of obstructive jaundice similar to that caused by carcinoma in the same site. A case of this type has

been described by H. B. Robinson. Pressure on the inferior vena cava may give rise to venous obstruction in the lower part of the body with oedema. Careful palpation of the abdomen may reveal a tumour or tenderness in the region of the pancreas.

OESOPHAGUS

Though frequent in the region of the mouth, pharynx, &c., syphilis is very rare in the oesophagus, stomach, and intestine, becoming frequent again in the rectum.

Syphilis of the oesophagus, notwithstanding its rarity, has long been known, having been described by Marcus Aurelio Severino (1580–1656). Nothing is known of an acute process. Gummata have been described, and ulcers have been found, chiefly in the lower part.

STOMACH

Incidence. In ninety-eight post mortems on subjects of acquired syphilis, Chiari found only one undoubted case. Flexner in 1898 could only find in the literature fourteen trustworthy cases: five of these were of the inherited form, nine were of the acquired.

Morbid Anatomy. An acute syphilitic gastritis has been described, but little is known of it from the anatomical standpoint. Virchow first described a chronic syphilitic gastritis, which consists in a cellular infiltration and increase of connective tissue of the walls. Flexner and Hemmeter have both described cases of diffuse syphilitic gastritis. Microscopically there is a small round-cell infiltration of the stomach walls.

The relation of syphilis to ulcer of the stomach is viewed by some authors as being a very close one, some (Lang) estimating syphilis as being the cause of the round acute ulcer in 20 per cent., the ulceration following the necrosis consequent upon syphilitic endarteritis. Others again consider that ulceration is never produced except as the result of the breaking down of a gumma of the stomach wall.

Gummata of the stomach have occasionally been described. Five or six of fourteen cases collected by Flexner from the litera-

ture had gummata. They mostly affect the stomach as well as the intestine. They produce flat plate-like thickenings which early form cicatrices. Ulcers and gummata may exist side by side. There may be several. They spread outwards from the submucosa. The muscular layer becomes hypertrophied and the serous layer may be thickened. The gummatous process instead of being circumscribed may be diffuse. Occasionally, owing to syphilis of the stomach, there are found circulatory disturbances both in the stomach and liver. The veins were specially affected in a case of Fraenkel's.

Symptoms, &c. The experience of any physician with syphilis of the stomach must necessarily be very small. In no known instances has a diagnosis of gumma of the stomach made during life been confirmed post mortem. The following case is reported by Lafleur²⁹: The patient, aged 37, had had syphilis ten years before. For about six months he had had very severe stomach symptoms, frequent vomiting, but very little actual pain. He had lost thirty pounds in weight. There was no hydrochloric acid in the gastric juice. Although his colour was good he had become very thin and weak. The stomach was moderately dilated, there was visible peristalsis after inflation, and there was a great difference in the consistency of the stomach wall as the waves of peristalsis passed. An exploratory operation was done by Dr. Armstrong of Montreal. There were perigastric adhesions and an extensive area of ulceration fully four inches in extent along the anterior wall. The edges were undermined, the surface smooth and almost bloodless. Dr. Lafleur suggested the specific nature of the ulcer and the patient was given anti-syphilitic treatment. He gained rapidly in weight, there was no recurrence of the vomiting, and he has remained well ever since. The special features of the lesion, the soft overhanging edges, the dry and bloodless base and the long tag-like adhesions on the external surface suggest that the condition was not one of simple ulcer. This appearance, together with its microscopical structure, is almost identical with that described and figured by Flexner.³⁰

Flexner's case was in the Johns Hopkins Hospital on several

occasions. He was first admitted in February, 1893, when he was 48 years of age. He had had a primary sore ten years before. In January, 1890, he had irregular fever with pains in the abdomen. His evening temperature was sometimes as high as 103.5° . He gradually recovered. In July, 1892, he had diarrhoea, and the legs and abdomen became swollen. The dropsy only disappeared in November, at which date he had lost nearly eighty pounds in the previous two years. There was no jaundice; the liver could not be felt, and the spleen was enlarged. The case was regarded as one of ordinary cirrhosis of the liver. He returned early in 1894; in the interval the abdomen had been tapped forty times. The spleen was greatly enlarged. In November, 1894, he returned again. He had been tapped up to date sixty-five times. He had been taking potassium iodide freely and had been gaining in weight. One day he had sudden pain in the abdomen, signs of acute perforation, and he died of peritonitis. At the post mortem, the liver was reduced in size, particularly the left lobe, which was reduced to a shrunken mass formed by the confluence of several gummata forming a fibrous tumour 11 cm. by 5 cm. It extended into the right lobe. The spleen was enlarged and hard, measuring 12 cm. by 17 cm. In the greater curvature of the stomach was an open ulcer 5 cm. by 5 cm., with puckered, overhanging margins and a central perforation. The condition is well figured in the original paper by Flexner.³⁰

Syphilis of the stomach may produce a palpable tumour. At the pylorus or near, there may be nodular thickening, and those cases in which tumours have entirely disappeared may have been syphilitic in origin. Some cases recorded by Einhorn are probably of this nature. Again, following the scar of a syphilitic ulcer near the pylorus the orifice may be narrowed so as to give rise to dilatation of the stomach. In one group of cases a tumour believed to be in the stomach is really due to a gumma of the left lobe of the liver adherent to the anterior wall of the stomach. These cases simulate very closely carcinoma of the stomach.

INTESTINE

The duodenum may be attacked with the stomach. The most frequent region for the small intestine to be affected is in the lower part of the jejunum. The colon alone has been found to be the seat of the disease, but it is in the rectum that syphilitic affections are common; in the rest of the intestine they are extremely rare. The intestine is attacked both in the hereditary and acquired forms. The conditions which have been described are acute catarrh, which has no features which serve to distinguish it from other forms of inflammation of the mucous membrane; the lymph follicles swell up and may give rise to small ulcers. A chronic form of enteritis has been described with ulceration and extension of the disease deep into the muscular coats.

Perhaps the most frequent lesion is ulceration and its consequences. Fresh gummata are but rarely seen, and ulceration is almost always the result of a breaking-down gumma, which, owing to the contents of the gut and often to post-mortem change, is natural. E. Fraenkel³¹ has described a condition of jejunitis with peritonitis in a five-days-old premature male child. The affected part of the intestine was in the form of a bunch of coils which, owing to firm adhesions, could not be unravelled. The liver, spleen, kidneys, &c., were unaffected—the peritoneal cavity contained 100 cc. of reddish, slightly thick liquid and the peritoneal surfaces showed flakes of lymph. Sections of the intestine showed necrotic areas involving the greater part of the thickness of the wall of the gut, and ulcers; both of these changes were independent of lymph follicles. Spirochaetes were extremely numerous; but except for these there were no histological features which would serve to distinguish this form of inflammation from others, such as tuberculosis.

Cicatrices often encircling the greater part of the bowel are frequent after syphilitic ulceration; the scarring invades a considerable thickness of the muscular wall. Obstruction, partial or complete, has been described. Perforation may follow ulceration. Amyloid degeneration of the small intestine may occur. It is commonest in the lower part of the jejunum. It has been

suggested that syphilis accounts for a proportion of the cases of appendicitis, but it has yet to be shown that appendicitis is more frequent in syphilitics than in other patients.

Rectum. The special liability of this part³² is partly due to direct infection by the secretion from the vulva or from condylomata. On this account the disease is much more frequent in women than in men. Ulceration is the commonest lesion, the result of the breaking down of a gumma. The loss of substance, frequently very extensive, is usually circular and in healing leads to marked stenosis. There may be no symptoms attaching to the stage of ulceration, so that the patient may not be seen until narrowing has taken place. In the stage of activity the bowel is greatly thickened, the muscular coat is much hypertrophied, the mucosa roughened, or actually ulcerated, and the lumen narrowed so as to admit the little finger with difficulty. Periproctitis is commonly a sequence, and the pelvic peritoneum may be greatly thickened. The ulcers may perforate either into the pelvis or vagina. The diagnosis is rarely difficult though the syphilitic rectum has been excised for carcinoma. The most important points in this respect are the greater frequency in women, the marked thickening of the walls, the narrowing of the lumen, and the absence of a hard raised edge to the ulcers. The presence of syphilitic lesions elsewhere, a history of frequent miscarriages, or evidence of syphilis in the husband may also help to establish a diagnosis. A remarkable form of syphilitic tumour of the pelvis has been described in which the pelvic fascia is chiefly involved, forming a dense mass in which the organs are embedded. Herxheimer³³ cites four cases from the literature and adds one of his own. The mucous membranes may be intact. In one instance the pelvis was occupied by a tumour the size of two fists situated between the bladder and rectum, which during life was thought to be cancer.

CHAPTER VI

SYPHILIS OF THE LIVER

Incidence. The difficulties attending the recognition of certain forms of hepatic syphilis, especially those in which the sclerotic element is marked, are very great. In different centres the personal element of the investigator in respect of what he considers to be evidence of syphilis has to be considered. During a period of eighteen years at the Johns Hopkins Hospital there were thirty cases diagnosed during life; in the post-mortem room, out of 2,500 autopsies there were forty cases showing gummata or syphilitic cicatrices (twenty of each) and fifteen additional cases regarded as syphilitic cirrhosis. In the 5,088 post mortems analysed by Flexner at the Philadelphia Hospital, interstitial changes were found in forty-two, gummata in twenty-two, perihepatitis in sixteen, amyloid degeneration in seventy, syphilitic scars in thirty-eight. In the post-mortem records of St. George's Hospital during a period of forty-two years, out of 11,629 autopsies there were thirty-seven cases of gummata and cicatrices were found in twenty-seven other cases. The incidence of congenital syphilis is much higher, especially in the case of infants dying under one year.

MORBID ANATOMY

a) *Acute necrotic hepatitis* may occur either as a general or local process in the liver. In the former case it occurs in cases of acute yellow atrophy the result of syphilitic infection. The liver is reduced in size, its surface is smooth, but if the illness has lasted some time small nodules may project due to hypertrophied liver tissue. The capsule is wrinkled and the greenish-yellow colour of the liver shows through it. The organ is very flabby. On section the substance of the organ is soft but not easily broken down; it is bright yellow with occasional areas of

a more reddish tint. Occasionally crystalline bodies may be seen on section, e.g. leucin and tyrosin.

When the process is more local it may be seen in an otherwise normal liver, but more usually there are changes elsewhere in the shape of gummata, cirrhosis, or perihepatitis. These necrotic patches, which are as a rule reddish areas surrounded by a zone of hyperaemia, may be compared to the areas of necrosis seen in typhoid fever.

Histologically, in the more generalized form the liver substance is hardly distinguishable, the cells are either necrotic with badly staining nuclei, or distended with large fat globules, or, in places where the process is less advanced, containing numerous small granules. Haemorrhages are frequently present. The interstitial tissue is made up of necrotic portions of cells and a small-cell infiltration with the remains of blood-vessels and connective tissue. When less advanced and the lobulated structure is still visible, the process is seen to be most advanced in the periphery of the lobule and passes inwards towards the intra-lobular vein. The bile passages and smaller bile-ducts are in a condition of catarrhal inflammation. Essentially the same change may be present in patches in livers either with pericellular cirrhosis or with the cicatrices of old gummata.

(b) *Gummata* may be seen in the livers of syphilitic subjects in various stages. The acute local necrotic hepatitis just described is probably the earliest form. A fully developed gumma consists of a firm yellowish-white substance surrounded by a ring of fibrous tissue which spreads for some distance into the neighbouring liver tissue, often in a radiating manner. Three zones may be distinguished—first, the central cheesy necrotic tissue; secondly, the fibrous layer; and thirdly, the zone of fibrous tissue invading the liver substance, often showing an increase in the number of vessels, and hence of a reddish colour. In the case of older gummata there is a firm greyish-white connective-tissue capsule, marking it off clearly from the liver tissue on the one hand and the caseous portion on the other (Plate XVII).

In still older gummata the contraction of the fibrous capsule and the absorption of the outer caseous portions cause a retrac-

tion in the neighbouring parts of the liver, and this is especially well marked when the gumma is near the surface. Other changes seen are calcification, softening of the caseous matter due in some cases to septic invasion, in others possibly to iodide medication.

They may be either single or multiple, and when multiple they may be present in small numbers of different sizes and stages. The best examples of multiple gummata are in congenital syphilis, where minute miliary gummata (Plate XVIII) are distributed evenly throughout the organ. This will be described later.

The microscopic appearances of older gummata are not different in type from such structures elsewhere. The central portion is occupied by necrotic tissue staining badly, the result partly of the syphilitic toxin, partly of the associated endarteritis; outside this is a layer of inflammatory cells, chiefly round cells, with some giant cells, the result apparently of the fusion of young connective-tissue cells. Giant cells are not so numerous or of the same type as in tuberculosis; they contain only a few nuclei not arranged in any constant manner. Amongst this tissue, if the lesion is a recent one, or the part examined an advancing edge, are to be seen the remains of liver cells, some shrunken but still stainable, others necrotic and staining badly. Further outwards are the connective-tissue elements, some of which are epithelioid, others, where the lesion is stationary or retrogressive, of the adult type of connective tissue. The number of new vessels in the more recent portions of granulation tissue is greater than in a tuberculous lesion. The fibrous capsule of an old gumma contains elastic tissue, which may account for its distinctive consistency as compared with other forms of granulation tissue. Osmic acid stains both the necrotic portion and globules in the capsule.

The fibrous tissue of more advanced gummata is lamellar in structure, scattered through which are round cells. It invades the portal spaces and often sends rounded prolongations into the substance of the lobules. In certain parts the structure is that of a biliary cirrhosis.

The vessels surrounding an hepatic gumma of recent origin

show characteristic changes (Plate XX). The branches of the portal veins are thick and deformed, when seen in cross section, by peri- and endophlebitis. Moreover, the arterioles of the hepatic artery present periarteritis and endarteritis in a marked degree, almost obliterating in many instances the lumen of the vessel.

Gummatous cicatrices. Just as gummata may be single or multiple, so may the scars indicating their previous existence; and as tertiary syphilis is a recurrent disease, scars of old gummata may coexist with active gummata, and all possible transitions from the gumma to the cicatrix may be seen. The single gummatous cicatrix may affect the left or the right lobe, more often the former, or the region in the neighbourhood of the portal fissure. The left lobe may be reduced to a mere nodule of liver substance attached to the rest of the organ by means of scar tissue. On section a scar, if near the surface, shows a thickening of the liver capsule and strands of fibrous tissue stretching out into the more normal liver substance. The fibrous tissue of the sections of the portal spaces in the neighbourhood shows some increase.

The scars may be peripheral or central. When many are present the organ consists of a number of rounded masses, giving rise to the appearance which is termed the botryoid liver (Plate XIX). In this case the depressions are the scars and the elevations the hypertrophied portions of the remaining liver tissue.

Cicatrices may produce stenosis of the common bile-duct, the cystic duct, or the hepatic duct, leading to secondary cirrhotic changes; or there may be interference with the vascular supply, leading to localised stasis or naevi.

Histologically the gummatous cicatrix has very little to distinguish it. It consists of a mass of fibrous tissue having the usual staining reactions. There may be portions, especially when the fibrous tissue is of a looser texture, where an excess of newly formed vessels is seen; careful search may detect syphilitic arteritis or an artery undergoing absorption after thrombosis. The liver cells in the neighbourhood of the cicatrix may be partly separated from each other by extensions of fibrous tissue; some portions may recall the type of pericellular cirrhosis. The

cells themselves are atrophic in the neighbourhood of the scar tissue ; they may be large and deeply stained in the hypertrophic regions. Occasionally groups of cells, especially if isolated by fibrous tissue, may be seen undergoing necrosis.

Perihepatitis. This may vary from a small thickening of the liver capsule comparable to the 'milk-spot' of the pericardium to a marked thickening of the whole capsule, with complete adherence of the capsule to the abdominal parietes. The localised form is the result of a gumma either in the liver tissue itself or in the capsule. In the more recent cases of syphilis, especially in the congenital forms, the liver is often covered with patches of recent fibrinous exudation. These changes often lead to adhesions between the liver and other structures, as, for instance, the diaphragm, stomach, or colon, and it may thus lead to abnormal motility of the liver. Occasionally perihepatitis precedes the affection of the liver substance.

Amyloid change may be general or local ; in the general form it occurs both in congenital and acquired syphilis, and is indistinguishable in its anatomical features from the general amyloid change produced by other causes. The liver is larger than normal, its capsule is stretched and the borders are rounded. The cross section has a transparent look, and gives the usual amyloid reactions with iodine and sulphuric acid. Amyloid reactions may sometimes be detected in the liver tissue adjacent to gummata and cicatrices.

Syphilitic forms of Cirrhosis, Interstitial Hepatitis of Congenital Syphilis (Pericellular Cirrhosis). The changes present in the livers of infants dying from congenital syphilis must be looked upon as a secondary manifestation. The liver is usually of normal shape, but large, and constituting one-twelfth to one-sixteenth of the body-weight instead of one-twenty-fifth ; one lobe may be atrophied. The surface is firm, and may be smooth or with evidence of perihepatitis of recent origin, or having given rise to adhesions. The colour may be uniform throughout or patchy, and little evidence of lobules may be present ; congested in the early stages of the disease, it becomes lighter later on, and its most usual tint is a yellowish grey, suggesting that of certain types of flint (Foie

silix of Gubler). With this yellow tint there is often a transparent appearance suggestive of amyloid disease. Scattered over the whole cut surface, or only in certain parts, may be seen minute whitish dots, the so-called miliary gummata, which in their appearance have been compared to semolina grains. They have almost the same appearance as miliary tubercles, differing only in being more opaque (Plate XVIII).

Microscopically, in the parts where the changes are earliest there is congestion and an infiltration with round cells. This infiltration becomes more diffuse and spreads between the liver cells. The fixed connective-tissue cells also take part in the cell proliferation, namely the endothelium cells of the capillaries and lymphatics and the connective-tissue cells of Glisson's capsule, which is increased in amount. At a later stage the congestion and round-cell infiltration disappears, the fibroblasts become adult connective-tissue cells, the liver cells now being isolated by well-developed fibrous tissue (Plates XXI and XXII). The liver cells are small and often contain much fat. In the so-called miliary gummata the central portion is formed by necrotic homogeneous substance, in which is embedded an occasional polymorphonuclear leucocyte or round cell; round this is a zone of inflammatory cells, some with polymorph nuclei, others with round nuclei. Outside this is the hyperplastic zone with the isolated liver cells.

Cirrhosis. Both in the congenital and in the acquired form cirrhosis of the liver may be the result of the syphilitic affection. There are two forms which more readily lend themselves to description, but no sharp line of demarcation exists between them, nor between cirrhosis due to gummata on the one hand or true syphilitic cirrhosis on the other. The first form is that in which the deposition of fibrous tissue is more specially inter-acinous, giving the appearance of a monolobular cirrhosis. To the naked eye the bands between the lobules can easily be distinguished from the liver tissue, which is paler, from fatty degeneration, than normal. The liver is usually diminished in size. Microscopically, there are more new vessels in the fibrous tissue than in other forms of monolobular cirrhosis. There may be

a great increase in the number of new bile-ducts. Here and there at the edges of liver lobules the structure may recall the type of pericellular cirrhosis.

The second form is hardly at all to be distinguished from Laennec's cirrhosis. The liver is small, with nodular projections on the surface, and the capsule thickened. On section, the organ is made up of isolated rounded masses of liver substance, which may be yellow from fatty change or bile-stained, separated from each other by thick strands of fibrous tissue.

Histologically, the liver cells may be necrotic or undergoing fatty change. Amyloid changes may coexist. In the fibrous tissue there may be evidence of thrombosed vessels undergoing absorption, or an occasional small artery may be affected by a true syphilitic arteritis.

Other changes met with in syphilitic livers are : Thrombosis in one of the venous systems of the liver ; it has been noticed in the portal veins, in the hepatic veins and inferior vena cava. Rupture of gummata into the peritoneal cavity has been described. Infarcts producing atrophy of an area of liver substance have been seen.

CLINICAL MANIFESTATIONS

In about 5 per cent. of cases of tertiary syphilis, exclusive of amyloid disease, symptoms are referable to disease of the liver. Not all syphilitic conditions of the liver give rise to symptoms : a gumma may exist and be palpable, but yet be found accidentally ; only when gummata are large do they give rise to constitutional symptoms. A large number of cases are those in which there is either a general cirrhosis of the organ or those in which the scars of previous gummata alone remain, as in the following case :—

Thos. M., aged 24, was admitted to Montreal General Hospital May 4, with extensive erysipelas of the head, and died May 16. The patient had two bone ulcers on the forehead which had been attacked by the acute erysipelas. The condition of the internal organs was negative with the exception of the liver, which weighed 78 ounces, was firm, elongated, particularly in the left lobe,

the extreme width of which was 8 inches, while the right lobe at the gall-bladder measured only 6 inches. The capsule was slightly thickened, particularly in the neighbourhood of the suspensory ligament. On the surface of the right lobe were four or five puckered depressed cicatrices, showing in the centre healing gummata.

Previous affections of the liver, such as alcoholism and malaria, appear to have a predisposing influence ; perhaps this is a reason why syphilis of the liver is more frequent in men. Gummata of the liver are very rare in cases showing the parasymphilitic lesions of syphilis, such as locomotor ataxia.

(1) *Symphilitic Jaundice*. Apart from the form which occurs in the tertiary stage due to gummata, jaundice occurs in the secondary stage. It is a somewhat rare complication, being present, according to Werner, in 57 out of 15,799 cases of syphilis, i. e. 0.37 per cent. It is more frequent in women. Gubler, in 1853, by clinical observation first proved the condition to be syphilitic.

The cause has been ascribed to duodenal catarrh, to the pressure of enlarged glands on the bile-ducts, to the giving of mercury, to affections of the blood-vessels in the portal canal, and to catarrh of the smaller bile-ducts, of which the last is the most probable. Mercury is certainly not the cause, for the disease is cured by antisymphilitic treatment. Post-mortem evidence is required before its cause can be accurately stated. It occurs suddenly and often simultaneously with the rash, which in these cases is pronounced ; it is seen between the fifth and the sixth week after infection. The gastro-intestinal symptoms of catarrhal jaundice may be absent ; the jaundice lasts from three to four weeks, unless treated it may become chronic, and if mercury be discontinued jaundice may recur. The liver may be slightly enlarged as well as the spleen. In one case mentioned by Quinke and Hoppe-Seyler³⁴ there was ascites with enlargement of the liver and spleen. The faeces are not completely colourless. Fever frequently accompanies the condition. Alimentary glycosuria has been observed (Bouchard), and is to be explained on the assumption of an interference with the glycogenic function of the liver.³⁵

(2) *Acute Yellow Atrophy in Syphilis.* There is little doubt that syphilis may be the cause of acute yellow atrophy, and, just as we may have in the secondary stage a mild infection of the biliary passages, so in the same period the infection of the liver may be an acute hepatitis which does not resolve. We may look upon the parenchymatous hepatitis which is here present in the same light as the areas of necrosis present in the liver in typhoid fever and other infective diseases.³⁶ Moreover, the acute disease may follow simple jaundice of the secondary period. Of Lebert's seventy-two cases of acute yellow atrophy, seven were due to syphilis. The symptoms appear gradually, with loss of strength and appetite and anaemia; vomiting and jaundice appear and, later, the cerebral symptoms of delirium, involuntary passage of urine and faeces: the urine contains bile, leucin, and tyrosin. The cases are always fatal, and seldom more than a week elapses after the appearance of the more serious symptoms before death. Specific treatment is of no avail.

(3) *Cases with Gummata showing Hepatic Tumours.* Two stages in gummatus affections of the liver may give rise to an hepatic tumour, first in the acute stage, when it may be of large size and long duration, and secondly, when the gummata have disappeared, so as to give rise to cicatrices producing the so-called botryoid liver, of which the nodular masses are to some extent hypertrophic. The cases include the congenital as well as the acquired disease. The symptoms are pain in the abdomen, indigestion, occasional attacks of jaundice, loss of weight, and some loss of strength. The tumour may consist of small rounded elevations on the uncovered surface of a very slightly enlarged liver, or it may be a large mass in an enlarged organ extending much below its ordinary limits, or it may be a large cake-like mass in relation with the liver (see Plates XXIII and XXIV).

The cases are often confused with cancer, either primary or secondary, hydatid disease, or malignant disease of the gall-bladder. The general health suffers most in carcinoma and least in hydatid disease unless suppuration is present. In all cases in which there is a suspicion of syphilis a full course of iodides

should be tried ; they are useless, however, when the tumour results from cicatricial contraction and isolation of a portion of the liver substance. The following case illustrates this type :—

Large Syphilitic Tumour of the Liver ; Gradual Disappearance under Iodide. On February 11, 1896, one of us showed to the third-year Johns Hopkins Hospital class Walter R. Y., aged 47, a cloth-finisher (Gen. No. 3895), who had been complaining for a year or more of progressive enlargement of the abdomen and pain in the right side. The family history was negative. He was a Scotchman who had served in the English army in the Mediterranean Stations, and in India. He had had syphilis in 1874, and secondary skin symptoms as late as twelve years after. He had often used alcohol to excess. He thought that the local trouble in the abdomen began as long as two years ago with an enlargement on the right side, and with pain, at first in the pit of the stomach, but now more over the region of the liver. He had never been jaundiced. In Philadelphia, where he resided, he was in the Jefferson Hospital in September, 1893, and in the Episcopal Hospital for sixteen weeks in the spring of 1894 ; but at that time the tumour, he said, was not so prominent.

He looked a healthy man, fairly well nourished. There were brownish scars on the shins. On examining the abdomen the attention was at once attracted by a marked prominence in the right hypochondrium below the costal margin, the greatest projection being midway between the navel and the costal margin. There was no redness over the swelling. It could be seen to descend somewhat with inspiration. On palpation the liver was greatly enlarged. The lower edge could be distinctly felt within a finger's breadth of the navel, and in the nipple line there was an abnormally deep notch. In the parasternal line, occupying a position midway between the costal margin and the navel, there was a smooth, rounded mass, evidently in the liver. The fingers could be placed beneath the edge of the organ, just above the navel, and then the tumour could be felt to begin about an inch and a half or two inches from this point. Above, when he drew a deep breath, the fingers could be placed between the

costal margin and the rounded border of the tumour. Towards the right the mass was a little irregular. It was entirely painless. The vertical liver dullness extended from the upper border of the sixth rib for $16\frac{1}{2}$ cm. The gall-bladder could not be felt. The edge of the spleen was not below the costal margin.

The patient had no nodes, no signs of syphilis anywhere, and the mass seemed rather larger and more prominent than is usual in gummata. Still he had such a well-defined history of syphilis that we decided to give him iodide of potassium. He said that the tumour had been aspirated once or twice in Philadelphia with negative results. The sketch (Plate XXIII) gives a very good idea of the size of the liver and of the position of the tumour mass. It was large enough to be seen at a distance, and lifted the skin prominently as a hemispherical tumour.

We saw the patient again on February 18, and on March 3 and on March 23. On the latter date we thought that the tumour mass did not stand out with quite as much prominence. The outlines were distinctly less definite. He had been taking iodide of potassium and he was ordered to continue it in twenty-grain doses. He did not return until November 11, when he came back for the purpose of reporting upon his extremely satisfactory condition. He had taken the medicine for three months. The pains had gradually lessened; the tumour had slowly disappeared, and he had been feeling quite well, having gained thirty pounds in weight.

The inspection of the abdomen was negative; he was very much stouter than he had been; there was no trace of swelling in the upper abdominal zone. The tumour mass had disappeared entirely. It is difficult to believe so prominent a mass could have gone so completely. The edge of the liver was to be plainly felt about 4 cm. below the ensiform cartilage. There was no roughness. In the parasternal line the margin was felt two fingers' breadth below the costal margin, and here felt decidedly irregular and rounded. In the nipple line the margin of the liver was fully three fingers' breadth below the ribs, and the edge was smooth and round. The edge of the spleen was not palpable.

On February 25, 1897, the patient returned for examination.

He looked in splendid condition, having gained altogether fifty pounds in weight in the year since he was first seen. He was so stout that it was very difficult to make a careful examination of the liver. The enlargement in the epigastric region had apparently disappeared completely. The edge of the liver there could not be felt. Only just beyond the parasternal line, as one passed outward, one could feel just below the costal margin a hard firm border. Just beyond the nipple line the edge of the liver could be felt two fingers' breadth below the ribs. The edge of the spleen was not palpable.

(4) *Cases imitating Cirrhosis.* Ascites is the important symptom; the fluid may be chyloform owing probably to pressure on the thoracic duct or receptaculum chyli. Jaundice, as in alcoholic cirrhosis, is infrequent, and the other symptoms, haematemesis, dilated abdominal veins, and dyspepsia, are less frequent than in alcoholic cirrhosis. Epigastric pain is common and oedema of the legs is often associated with early ascites. In Hilton Fagge's and Andrew's cases the picture was that of acute yellow atrophy. If the symptoms are due to an active gumma, iodide of potassium will cause absorption, but if due to cicatricial tissue the remains of a gumma, the resemblance between alcoholic cirrhosis and syphilis becomes very close. Careful search must be made for other evidence of syphilis elsewhere, and attention paid to the shape of the liver, large irregularities favouring syphilis. The presence of an enlarged spleen is not of much help, for, though frequently enlarged in hepatic syphilis, it is also enlarged as the result of chronic alcoholism. In cirrhosis the patient is usually ill nourished, while in syphilis his nutrition may not have suffered. The following report illustrates many important points in the history of hepatic syphilis:—

Syphilis of the Liver. Ascites, recovery; Cerebral Syphilis, recovery. Pregnancy; sudden death—autopsy. Emma S., aged 33, admitted March 17, 1892, complaining of pains in the right side, and swelling of the abdomen. Her family history was good. The patient was herself very strong and well. She was married at 23, and had never been pregnant. She has never had a rash on the skin, or sore throat. Three years ago

she had jaundice and the abdomen was swollen. Two winters ago she had rheumatic pains and lumps on the shins. Her present illness began in July with pains in the back, tired feelings, and gradual swelling of the abdomen, legs, and feet. The swelling of the abdomen was severe, so that she had to be tapped, and between September and the end of December this had to be repeated several times. Since Christmas the swelling had not increased very much, and she had been troubled chiefly with pain in the right side, which was made much worse by walking. She had been slightly jaundiced at times. Her appetite was good; the bowels had been regular. For two weeks past the abdomen had been increasing in size.

Present condition : She was a small-framed, somewhat wasted woman ; the complexion was sallow and not yellow, the conjunctivae white ; the lips and mucous membranes were of good colour ; the tongue was clean ; the respirations were quiet ; the temperature was normal ; the pulse 106, of fair volume, and low tension. The cornea were clear, the teeth good ; and she had not a syphilitic facies. The superficial glands were not enlarged ; those in the posterior cervical triangles were just palpable. The left clavicle seemed a trifle larger than the right, and was a little irregular about the middle of the shaft. Both ulnae were a little enlarged ; the left tibia was much expanded in its lower third, and about the junction of the middle and lower third there was a rough, irregular elevation. The right tibia also seemed somewhat expanded in its lower half. There was marked tenderness in the shafts of both femurs.

The lower zone of the thorax was enlarged by the abdominal distension. The sternum was prominent, particularly at the junction of the manubrium and gladiolus. Expansion was equal on both sides. The percussion note was good throughout. Respirations were clear and no adventitious sounds were heard.

The apex beat was visible and palpable in the fourth interspace inside the nipple line. The sounds were loud, and in the recumbent posture there was a soft systolic murmur over the whole of the cardiac area, loudest at the second left cartilage, and in the erect posture heard only in this region.

The abdomen was considerably distended. In the median line could be seen just below the navel seven scars of the tappings referred to. There was movable flatness and some ascitic fluid remained in the abdomen. The abdominal walls were loose and flaccid. There was a small umbilical hernia. In the left upper quadrant of the abdomen just below the costal margin a well-marked ridge was seen, which on palpation was found to be the border of the spleen, extending downwards nearly to the crest of the ilium, and forwards nearly as far as the nipple line. The margin of the liver could be felt 8 cm. above the navel, and could be traced to the left beyond the median line. In the nipple line a distinct notch could be felt. The surface was distinctly irregular, though there were no marked prominences. The upper limit of the liver dullness was at the base of the xiphoid cartilage, at the fifth rib in the parasternal line, at the sixth in the mammillary line, the seventh in the anterior axillary line, and the eighth in the mid-axillary line. The right kidney was not palpable. The urine was amber-coloured, sp. gr. 1.016, contained no albumin, but a few hyaline and granular casts were seen. The patient was given Addison's pills, and iodide of potassium, twenty grains three times a day. The urine increased very much in quantity, the abdomen became less distended, the general nutrition improved rapidly, and she increased in weight, from 100 pounds on March 19 to 113 pounds on April 4. She was discharged on April 13. The diagnosis was syphilis of the liver.

The patient was readmitted June 28, 1892. She stated that she had not taken medicine since she left the hospital. She felt well until three weeks previously, when she began to have headache, nausea, and vomiting. The pain in the head was constant, not worse at night. She had felt very dull and stupid, and the least talking made the headache much worse. About three weeks ago she partially lost the use of the left hand. For two weeks she had been in bed. Her mother stated that she once fainted and had a sort of spasm. She had pains in the shoulders and back, but no swelling of the abdomen.

On admission the patient was dull, drowsy, and complained only of headache. She had no fever. The tongue was thickly

coated ; the pupils were equal, responded to light and accommodation. There was a double optic neuritis. The movements of the facial muscles were equal. No disturbance of sensation in the skin of the face was detected. The muscular development of the arms was equal ; the muscular power of the flexors and extensors of the left arm and hand seemed to be slightly diminished. There was no paresis of the legs ; the deep reflexes were not increased on either side. The abdomen was not distended and there was no ascites. The spleen was still enlarged, and could be seen in the left hypochondriac region. The edge of the liver was not so low as before and the border was not to be felt so distinctly, but it was still irregular. On July 4 there was slight left-sided strabismus. She was dull and heavy. She was given iodide of potassium freely, and she improved rapidly, gaining in weight, the slight paresis of the left arm disappeared, and she went out feeling strong and well.

On November 3 the patient was again seen. She looked well and fat. There was no ascites. The navel was thick and prominent. The edge of the liver was just palpable two fingers' breadth below the costal margin in the upper sternal line, and was just at the costal margin in the nipple line. In the epigastric region, just below the ensiform cartilage, on deep inspiration both the surface and edge of the liver could be felt to be irregular. The spleen was still enlarged and could be felt a full hand's breadth below the costal margin. The tibia and fibula on the left side just above the ankle presented recent nodes, which were tender.

One day in May, 1903, the patient returned in great distress, saying that the dropsy had come back and that she was getting larger and larger. She looked very well, and on examination the distended abdomen was found to be due to pregnancy. We were so interested in her case that she was admitted so that she could be confined in the hospital. She remained very well, but on July 3, a few days before she expected to be confined, she was found dead in the water-closet.

Autopsy. August 1. Abdomen enormously distended, measuring 110 cm. in circumference, and there was a redundant patch of

skin at the umbilicus, corresponding to an old hernia. There was moderate oedema of the legs. On exposing the peritoneal cavity the uterus was seen to occupy almost the entire abdomen.

There was no effusion in the pleurae; the heart was not enlarged and weighed only 310 grams. The left ventricle was contracted, and the right side of the heart was much distended; there was slight thickening of the aorta in the neighbourhood of the valves; the mitral valve was $9\frac{1}{2}$ cm. in circumference; length of left ventricle was 8 cm.; the thickness of its walls 15 mm. The lungs were crepitant throughout and the bronchi contained much frothy mucus.

The liver weighed 3,200 grams; its dimensions were 27 by 22 by $10\frac{1}{2}$ cm. There were many old firm adhesions between the capsule and the diaphragm, the spleen, the stomach and omentum. The surface of the liver was puckered and depressed in many places; the largest depression was on the upper surface of the right lobe, just above the gall-bladder. There were also old cicatricial scars on the under surface, especially of the left lobe. The capsule showed irregular areas of thickening, in some places almost cartilaginous. The veins below the capsule were distended. The general colour of the organ was mottled, dark bluish red in the depressions, while the elevated areas varied from a light yellow to a reddish grey. On section the organ was divided into coarse, multilobular areas, separated by lines of connective tissue. In some places there were opaque, yellowish-white nodules, sharply circumscribed, slightly elevated above the surface. Corresponding to the scars on the surface there were in the substance irregular puckerings, showing radiating lines of greyish-white connective tissue. The gall-bladder was surrounded by adhesions. The bile was yellowish brown, transparent, and contained no concretions. There was no note as to the condition of the portal vein or the gastro-hepatic omentum. There was a diverticulum of the lower end of the oesophagus about $2\frac{1}{2}$ cm. in depth. There was a cicatrix of an old ulcer 2 cm. from the pyloric orifice. The kidneys were enlarged; one reddish in colour showed fine fatty degeneration and marked parenchy-

matous changes in the secreting tubules. There was a nodular gumma in the left kidney.

Cirrhosis of liver (specific). J. C. K., 19, Jonesboro, N. C., seen with Dr. W. A. Monroe, Sanford, N. C. In April of this year swelling of the abdomen began; he was said to have malarial fever, it got larger and larger, he became short of breath, and had a weak pulse. There was no pain and the liver was enlarged. There was heart trouble.

His father was a distiller. The boy had taken whisky for a year or so. Four years ago he had a sore on the penis, it did not last long, but the doctor said that several cases of syphilis came from the same source. In his case there was no discharge, only the sore. Another man had been infected by the same woman. He had never had rheumatism—had been very healthy—always well—could run about and was never short of breath. The trouble came on gradually and he was not laid up in bed.

The patient looked healthy, his colour was good, tongue clean; he was not at all sallow, there was no jaundice, and the pupils were widely dilated. The pulse was rapid, tension good, not increased; the vessel was just palpable. His greatest measurement had been 41 inches. The ankles had once been a little swollen.

The abdomen was large, with well-marked atrophic striae, placed irregularly, and red and fresh looking. The abdomen was fairly uniform, showed a transverse groove just above the navel. The ensiform cartilage was tipped up. Measurement from its tip to the navel was $9\frac{1}{2}$ inches, from navel to pubic bone 7 inches. The prominence was unusually marked in the epigastric region. Here evidently the intestines had floated up. Fluctuation was everywhere very distinct. The abdomen was moderately tense. In the epigastric region, and in the hypochondriac region, one could on dipping feel a hard edge and surface, probably that of the liver. The spleen was not palpable, no nodular masses could be felt anywhere. Percussion everywhere was flat, except in the prominent epigastric region. There was well-marked movable dullness. The cardiac impulse was pushed up. The area of dullness was not

increased. The heart sounds were clear, the second being reduplicated at the pulmonary area. The most marked pulsation was in the third interspace, close to the sternum. The lungs were clear in front and behind. A few crackling râles were heard at the bases. The teeth were good. The facies was not luetic; the shins were clear, and there were no nodes.

On December 14, 1896, his doctor called. The boy was tapped three times at intervals of a month and a half. He had been taking iodide. He had a chill, had been up and about, and his colour was better. There was still some fluid in the abdomen. The liver was still enlarged, to be felt $10\frac{1}{2}$ inches from the costal border.

(5) *Cases resembling Chronic Splenic Anaemia.* Such cases may have marked anaemia of the chlorotic type, diminution of the leucocytes, and great splenic enlargement. Cases have been reported by Coupland and by Osler.

(6) *Cases resembling Leukaemia.* This type is extremely rare and little known; the following case is an example:—

Syphilis of the liver. Great enlargement of the spleen. Great enlargement of the peripheral lymph-glands. Leukaemia.

Sarah S., aged 23, admitted November 11 with ascites.

Family History: Her father died of pneumonia ten years previously; her mother was living and well; two sisters were living and well.

Personal History: She had been a very delicate child, and did not walk until the fourth year. Eight years previously she had had some abdominal troubles, and her abdomen had been enlarged ever since. She was at that time in bed for half a year. From her twentieth year on she had been fairly healthy. Prior to that time she was always ailing.

Present illness: She stated she had been working up to two weeks ago, when she had a chill, a great deal of headache, and much pain in the left flank. She had shortness of breath and cough at night, and could not lie down. She brought up a blood-tinged, thick expectoration. She had had some fever; the bowels had been very irregular; she had had no vomiting, no sweating. She had not lost especially in weight of late.

Condition on admission : The patient was a small, delicately built, anaemic girl, with a very sallow facies. She sat up in bed, was unable to lie down on account of pain. The temperature was 103.5° , the pulse 120, respirations 36. There was marked deformity of the chest owing to a flattening of the right side from old disease. The left side of the chest was full and moved very freely. There was a marked curvature of the spine due to this old contraction, which was regarded as due to a chronic pleurisy.

The abdomen was distended, measured 78 cm. at the level of the navel. The enlargement was not symmetrical, but was more marked in the left flank and in the hypochondrium. There was also a distinct protuberance in the right hypochondrium. The superficial veins were slightly enlarged. On palpation the abdomen was sensitive, particularly on the left side, and at the edge of the ribs there could be felt a firm mass, which extended nearly to the left inguinal region. Towards the right a sharp edge could be distinctly felt. It was movable on bimanual palpation. There seemed no question at all that this body was the enlarged spleen. On the right side, occupying the epigastric and right hypochondriac regions and upper umbilical region, there was an irregular firm mass, which extended a little below the level of the navel. The edge was rounded and hard. Deep in the right flank and apparently connected with it there were two smaller masses to be felt. These descended with inspiration, and they were thought to be in connexion with an enlarged liver. The inguinal glands were perhaps a little larger than normal, and were very firm. The epitrochlear glands were enlarged and firm ; the glands in the neck and axilla were moderately enlarged, freely movable, nowhere matted together. The blood-count gave 2,234,000 reds per c.mm., and a ratio of white to red of 1 to 25 ; the haemoglobin was 28 per cent.

On November 14 the ratio of white to red was 1 to 16. The temperature fell from 103° on the 11th, and on the morning of the 14th was 99.5° . She complained a great deal of shortness of breath, vomited, and seemed from the outset very ill. The

urine was scanty, specific gravity 1,020, contained a small amount of albumin and a few hyaline casts. The pulse became very rapid; on the 15th and 16th she had nausea and vomiting, became unconscious on the 16th, and died early on the morning of the 17th.

Autopsy (Dr. Councilman). The external lymph-glands were enlarged and hard. The peritoneal cavity contained 200 c.c. of slightly bloody fluid. The lower border of the spleen was 11 cm. from the ribs. The mesenteric and peritoneal lymph-glands were moderately enlarged and hard. Both liver and spleen were surrounded by firm, fibrous adhesions. The liver was brownish yellow in colour, very tough and hard. It was divided into a number of nodular masses from the size of an apple to that of a filbert, some of them almost separated from the liver, and only connected with it by a thin pedicle. The greater portion of the liver was made up of an enlarged left lobe. The right lobe was divided up by bands of connective tissue into the nodular masses already mentioned. On section of the liver there were large bands of connective tissue which traversed it in different directions, and from which smaller bands were given off. The largest of these bands ran between the right and left lobes. There were in addition fibrous gummata which projected from the capsule into the liver substance, and in these were hard necrotic areas. The portal vein was dilated to double its normal size. The spleen measured 23 by 16 cm. The surface was covered by slight adhesions, but was otherwise normal. The surface of the section was firm, of a dark purple-red colour. Neither the trabeculae nor the Malpighian bodies were visible. The organ weighed 1,510 grams. The right lung was small and firmly bound down by old adhesions. In the lower part of the pleural cavity there was a cavity containing 70 c.c. of opaque, gritty, semi-fluid material.

(7) *Cases resembling gall-stones.* Jaundice may be the main symptom of the pressure of a gumma on the common duct or one of its larger tributaries. Accompanying this, attacks of pain similar to those produced by gall-stones may suggest the obvious diagnosis of cholelithiasis. A tumour may be found in the region

of the gall-bladder, which may further suggest the diagnosis. The history of the pain should be inquired into both as regards its type, whether it is severe, like gall-stone colic, and as regards its relation to the appearance of the jaundice. Operation should be delayed in these cases till potassium iodide has been administered.

(8) *Cases with the features of Lardaceous Disease.* These cases are anaemic, slightly puffy, perhaps slightly yellow, badly nourished, and have albuminuria. In the absence of any of the other causes of lardaceous disease a careful search should be made for evidence of deeply-placed syphilis.

The Diagnosis of Acquired Syphilis of the Liver. Three important aspects must be borne in mind. First, the knowledge that syphilis of the liver shows itself in a variety of forms; it is necessary to remember that syphilis may be at the root of such different aspects of liver disease as have just been detailed.

Secondly, the personal history of the patient must be carefully inquired into in order to elicit any suspicion of luetic infection; even though infection be denied the patient may still be luetic; the secondary symptoms may have been so slight as not to fix themselves on the patient's memory.

A careful search should be made for evidence of disease elsewhere which suggests syphilis; the different systems should be examined carefully, especially with the view of finding out anything syphilitic in nature. Thirdly, Wassermann's serum diagnosis of syphilis may be used. It is interesting to note that Esmein and Parun³⁷ have shown that the ascitic fluid from a patient who clinically was thought to be suffering from a syphilitic cirrhosis of the liver gave a positive reaction.

The Clinical Forms of Congenital Syphilis

Congenital Syphilitic Hepatitis. This type shows itself at that period after the infection before gummata are found in other cases of congenital syphilis in 39 per cent. (Hofmeister) to 65 per cent. (Feige).

The symptoms presented fall into three groups: First, those primarily associated with the digestive system; the child is fretful,

cries as if from pain, and suffers from vomiting and diarrhoea. The severity of this varies from a slight inability to take its accustomed food up to a complete inability to retain any nourishment at all; jaundice may be present. Secondly, those symptoms showing themselves in general nutritional disturbance: the child wastes, becomes anaemic, the skin becomes wrinkled and of an ashy-yellow colour. The third class of symptoms are those which are associated with syphilitic disease of other organs; the child is thin, the abdomen large in proportion and may be distended with fluid. If ascites is not present, the liver may be observed descending much further on respiration than it normally does. The spleen, too, may be obviously enlarged on inspection. Both spleen and liver are hard on palpation and may be tender on pressure. Perihepatitis may give rise to restriction of the abdominal respiratory movements, and, if the adhesions are not too extensive or too old, auscultation may reveal a friction rub over the liver or spleen.

Late Congenital Syphilitic Hepatitis. Following Barthélemy,³⁸ the following forms may be recognized clinically:—

1. The so-called congestive form is one which is little known from the side of morbid anatomy, owing to its not being often fatal and the inability of establishing a certain diagnosis. The patient suffers from gastro-intestinal symptoms which are prolonged indefinitely and resist all ordinary curative measures; there is wasting, pallor, perhaps a subicteric tint, and a slight sense of discomfort in the hepatic region with a definite enlargement of the liver. If a syphilitic lesion occurs elsewhere and the patient is put on potassium iodide, both troubles disappear, the liver receding to its normal limits. In a case reported by Virchow the liver showed no changes, death having occurred from an intercurrent disease.

2. Diffuse interstitial hepatitis, a cirrhosis more hypertrophic than atrophic. The onset is sometimes sudden, sometimes very slow in its appearance, often so slow that it is impossible to determine the exact beginning of the affection. With very slight symptoms one may be able to detect a considerable enlargement of the liver. After a more or less long latent period, according

to the individual, the patient enters on a stage in which the diagnosis can be made by the clinical manifestations. The young patient begins to lose his gaiety, his appetite, and his energy. Then follow pallor and wasting. There are digestive troubles, sometimes with pain, sometimes without. The pain is usually epigastric and probably caused by perihepatitis. There is sometimes troublesome distension of the abdomen and a sensation of weight in the right hypochondrium. The patients sometimes have colicky pains. Some have constipation and flatulent dyspepsia, others have diarrhoea and enteritis. In very young children vomiting may be so persistent that any food given is immediately brought up again. The anaemia and wasting increase, the skin becomes dry, wrinkled, earthy, bronzed or dirty yellow. A subicteric tint shows itself, and becomes accentuated little by little without ever being really jaundice. The wasting may be extreme and may suggest tuberculous disease; even at this stage cure is possible by antisypilitic treatment. If the patient receives no specific treatment ascites develops, slowly at first, later more rapidly. At other times ascites may mark the serious beginning of the disease, developing without pain, fever, or reaction—a kind of chronic ascites with no very great disturbance of the general condition such as is seen in tuberculosis. Paracentesis is followed by a re-accumulation of the fluid. The collateral circulation becomes quickly established, the difficulty of the circulation increases, oedema of the legs supervenes. Finally death takes place without jaundice, haemorrhage, or fever.

The liver, if it has been examined during life, is nearly always enlarged, and often extends to about half an inch above the iliac crest. Only if the trouble dates back a year or more is the liver found deformed or atrophied; sometimes its surface is irregular. Jaundice is rare, as in alcoholic cirrhosis and in late hereditary syphilis.

The collateral circulation shows itself in the prominence of the abdominal veins during the time both when the liver is hypertrophied and when it is undergoing cicatricial contraction. The hypertrophy seen in certain cases gives place, if the disease

continues, to atrophy of the liver. Perihepatitis is often present, or adhesions between the liver and neighbouring organs. The spleen is very much enlarged in all cases. Untreated, these cases run a protracted course usually ending in death. With anti-syphilitic treatment employed early there is a good chance of recovery, and the benefit is often surprisingly marked.

An intermediate form between this and the next may be mentioned here; it is a form in which the sclerotic process is associated with the formation of gummata. The symptoms differ hardly at all from those of the previous form, except in so far as they are more prolonged and less severe unless treated by specific remedies. The liver for the most part is lessened in volume, lobulated or fissured by the invasion of strands of connective tissue, which either themselves are cicatrices of old gummata or are connected with them. The gummata have a firm consistence of a yellowish colour, and they cut somewhat like cartilage even in their yellow centres. Perihepatitis, recent or old, may be present.

3. *The gummatous form.* The liver tends to retain its physiological functions like other organs, therefore a developing gumma may produce no symptoms which can be justly attributed to it, and the liver may be affected by large gummata and yet, if the patient has another serious disease, no attention is drawn to the state of that organ because of its function being more or less preserved.

The development of gummatous hepatitis is insidious, its course is latent, and if any other abnormal phenomenon is developed it is probably associated with another organ, e.g. frequently the kidney.

The liver is deformed, and it may be hypertrophied or atrophied; it is rounded, nodulated, and hard (Plate XXIV). The spleen is almost always affected at the same time, and is hypertrophied or indurated. Often there exists sclerosis in other organs, lungs, kidneys as well. It is these other lesions which aggravate the condition, for the hepatic gummata disappear under antisymphilitic treatment with the same rapidity that is seen in other organs, e.g. tongue, testicle.

The patients may be attacked several times by hepatic gummata, which yield to treatment by potassium iodide. Pure gummatous lesions yield to this treatment much more quickly than the slower-advancing forms of interstitial hepatitis or amyloid degeneration. Ascites is rare, and is associated more especially with the forms showing a large amount of new fibrous tissue. Jaundice is as rare as in hepatic sclerosis, and only appears when the gummatous lesion directly presses on one of the larger bile passages. The skin has an earthy subicteric or dirty-yellow tint.

4. *Amyloid Liver.* This is the most serious affection of the liver in hereditary syphilis, not because of the presence of the amyloid change, but by reason of the general state of health of the patient which allows it to come on; and when this can be diagnosed the prognosis is indeed grave. The onset is very insidious. There is no jaundice or oedema; except when renal disease exists as well, there is no ascites. The liver is very large and smooth. There is perhaps diarrhoea, but some cases show no digestive disturbances. As in other forms of amyloid disease, the liver is not the only organ affected. The spleen, the lungs, the intestine may be affected. The spleen may be so large that a form of splenomegaly is described which is essentially syphilitic. Death occurs from cachexia. A mixed form is sometimes seen in which amyloid change in the liver is accompanied by gummatous change. This form is also very fatal. The liver is irregular, and in the parts not affected by gummata or their cicatrices shows amyloid change. The spleen is hypertrophied.

The Diagnosis of Congenital Syphilis. The most necessary factor in arriving at a correct diagnosis is to be aware of the nature of the changes affecting the liver in hereditary syphilis.

Clinically, syphilitic disease of the liver may be confused with alcoholic cirrhosis. Cases have been reported (Murchison) of cirrhosis in children due to alcohol; children of the poorer classes are often given beer and even spirits as early as two or three years old, and there is no doubt that cirrhosis can result from alcohol in the child as in the adult, but in the absence of any such history alcoholic cirrhosis is highly unlikely in a child

from 5 to 13 years of age, in which years syphilitic cirrhosis is most frequent.

Without well-marked signs of congenital syphilis other causes of enlargement of the liver, such as rickets, tuberculosis, gastrointestinal infection, and the various forms of anaemia, must be borne in mind. As pointed out by Rolleston,³⁹ when jaundice is present from birth without any manifest signs of syphilis, simple catarrhal jaundice and congenital obliteration of the bile-ducts must be considered. The common hypertrophic cirrhosis is usually accompanied by jaundice; syphilitic cirrhosis is not.

The cirrhotic changes in the liver produced by antecedent malaria or dysentery must be of a sufficient intensity and continued over sufficient time to have produced such changes; the development of syphilitic changes is very insidious and slow.

Tuberculous changes are so rare that they hardly need be thought of; they can be seen in the post-mortem room in the form of miliary granulations or yellowish nodules. There is usually evidence of tuberculosis elsewhere, as, for instance, meninges, lungs, peritoneum, at the same time if tuberculosis affects the liver. The application of Calmette's or von Pirquet's tuberculin inoculation method would nowadays serve to distinguish some of these cases.

Again, leukaemia may possibly be confounded with syphilis; but in syphilis the haemopoietic organs are not affected in the same way, the spleen is not hard, the liver is not embossed, the lymphatic glands are not hypertrophied, and above all the white cells of the blood are not increased.

By far the most important element in diagnosis, however, is the detection of syphilitic affections in other organs, for which a thorough search must be made. These affections may conveniently be grouped according to the classical subdivisions of Fournier :—

(1) *Facies and type*—the patient is small in stature or even a dwarf. (2) *Bodily development* is below the normal for the age—sexual character may be undeveloped. (3) *The cranium* is abnormally large, ill shaped or irregular; the bones are irregular or insufficiently ossified, the bridge of the nose is depressed.

(4) There are bony lesions elsewhere, e. g. evidence of periostitis. (5) Evidence of secondary or tertiary lesions of the skin, e. g. scars about the mouth and arms, from condylomata. (6) The eyes may show the effects of keratitis or iritis. (7) The auditory apparatus may be affected either by internal or middle ear disease or by atrophy of the optic nerve. (8) The testicle on one or both sides may be atrophied. (9) The teeth may be Hutchinsonian in type.

Last but by no means the least important element in diagnosis is to ascertain by careful inquiry whether any evidence of syphilis can be obtained from the family history of the patient, either as regards his father or mother, or as regards his brothers or sisters.

SYPHILIS OF THE SPLEEN

In the secondary stages of the disease an enlargement of the spleen can usually be detected due to the same causes—namely, swelling and hyperaemia of the pulp—as produce swelling in other fevers, e. g. in typhoid. An acute syphilitic splenitis has been described by Moxon, and in the later stages of syphilis the spleen sometimes undergoes a general and painless enlargement. Mr. d'Arcy Power⁴⁰ records a case in which this enlargement led to the organ becoming movable. He removed the spleen and the patient made a successful recovery. Similar cases of syphilitic enlargement have been recorded by other observers.

Gummata are the most common. They may be simple or multiple, and may vary in size from extremely small nodules to sizes almost as large as those met with in the liver. They are frequently present when the liver also presents gummatous changes.

Perisplenitis is frequently seen in cases showing other evidence of a syphilitic infection. It is frequent in congenital syphilis associated with a slight amount of peritonitis elsewhere. In older cases the capsule is either locally or generally thickened.

Cicatrices. When these are present the organ is nearly always enlarged, and presents fissures and indentations in the same way

as seen in the botryoid liver. The organ may even be entirely divided into sections. It may be difficult to say whether a single cicatrix, especially if near the capsule, is a gummatous cicatrix or an old infarct. Clinically the enlarged irregular organ may present an abnormal amount of mobility.

Amyloid Spleen. Amyloid changes may be present, either confined to the Malpighian bodies—the so-called sago-spleen—or a diffuse process associated with enlargement of the organ. These changes usually occur in long-standing cases, particularly those with disease of bone and of the rectum. Clinically the degree of leucocytosis may be so great as to suggest leukaemia, for which many such cases are mistaken.

CHAPTER VII

RENAL SYPHILIS

Incidence. Morgagni first recognized that syphilis could attack the kidney. In more modern times we owe much to the studies of Rayer⁴¹ and of Herxheimer.⁴² It is difficult to obtain accurate estimations of the frequency of nephritis in syphilis. Except in the secondary stage in which the acute form, having special features, is well recognized, it is almost impossible to say whether the diffuse chronic lesions are primarily syphilitic or only the ordinary forms occurring in syphilitic subjects. Other causes may be at work. Over-indulgence in alcohol is a common vice in syphilitic patients, and to the over-zealous use of mercury has in some cases been attributed certain outbreaks of nephritis. In Speiss's figures⁴³ from the Charité Hospital, Berlin, amongst 220 syphilitic patients the kidneys were affected, post mortem, as follows :—

Amyloid degeneration	42
Parenchymatous nephritis	21
Sclerosis	18
Interstitial nephritis	16
Atrophy	11
Sclero-gummatous nephritis	7
Various inflammations only partly attributable to syphilis .	16

Morbid Anatomy. The lesions are very variable according to the intensity of the infection. Syphilis can produce all the anatomical varieties of acute and chronic nephritis. In the secondary stage the two kidneys may be affected simultaneously by an acute or subacute diffuse inflammation. Only rarely is acute nephritis observed in the tertiary period. In this stage, however, the kidneys are specially prone to amyloid degeneration

and gummata. For convenience of classification the following forms may be described :—

A. *Acute Syphilitic Nephritis*. It may be acute or subacute. In the former the kidneys have the typical appearance of the large white organs; they are much heavier than normal—in one case recorded by Chauffard and Gourand⁴⁴ they were twice the normal weight; on section the parenchyma has a pale grey homogeneous aspect, and the distinction between cortex and medulla is very badly marked. Histologically there is considerable destruction of the elements of the kidney structure. The convoluted tubules are the most affected, hardly a single one is normal; the convoluted tubules are expanded and filled with an albuminous coagulum; the epithelium is almost completely destroyed. The glomeruli are compressed by the exudate in Bowman's capsule. There is marked intertubular oedema and diffuse infiltration of lymphocytes. In the arteries there may be an early endarteritis and periarteritis. There is no amyloid degeneration.

In another form less acute there is nothing of an anatomical nature from which a diagnosis of syphilis can be made. The kidneys are large, firm, increased greatly in weight, sometimes a whitish grey, sometimes dark red, sometimes mottled. The capsule strips easily. On section the cortex is expanded, pale or greyish red. The pyramids are markedly red. Histologically the glomeruli are the most affected; they are increased in size, there is proliferation of the supporting cells of the glomerulus and the cells of Bowman's capsule. The convoluted tubules are more or less dilated, full of exudates of various types, and the epithelium is in a state of fatty degeneration. The arterioles are more or less affected according to the type of case. The connective tissue of the organ is undergoing great proliferation. Large numbers of lymphocytes are collected round the glomeruli and arteries. Masses of embryonic cells have been reported in these cases which have been looked upon as small gummata.

B. *Chronic Syphilitic Nephritis*. Between the former and this type there is no marked distinction, the cases graduate from one to the other imperceptibly.

(i) *Chronic Parenchymatous Nephritis* with amyloid degeneration. This is often the final stage in the subacute nephritis, but sometimes also a tertiary manifestation with an insidious onset. It is by far the most frequent form of renal syphilis met with (over 50 per cent., Bamberger⁴⁵). The kidneys are of normal size, sometimes perhaps slightly increased or diminished, pale and firm. The glomeruli and neighbourhood of the arteries have the appearance of amyloid degeneration, the reactions of which they show. Hyaline degeneration is also present. To these changes must be added those of chronic parenchymatous nephritis.

(ii) *Sclero-gummatous Nephritis*. From an anatomical point of view this type most markedly suggests syphilis, as it recalls the lesions met with frequently in the liver. The kidney has an irregular appearance, indented by cicatrices, at which spots the capsule is adherent; there is partial and irregular atrophy often unequal on the two sides; small gummata in variable numbers are distributed in the cortex or medulla or both; they are dry and encysted in fibrous tissue or undergoing softening. An amyloid change may sometimes be detected. Histologically there is a diffuse atrophic sclerosis with hyaline degeneration of the glomeruli and atrophy of the tubules; the epithelium of the tubules is in a condition of fatty degeneration, with marked endarterial changes sometimes to the extent of obliterating the vessel, and always sufficiently marked to effect an ischaemia of the portion of the organ supplied. In structure the gummata are the same as those met with elsewhere, and, indeed, the liver may be affected in the same manner at the same time. The heart may be hypertrophied.

(iii) Gummata, independently of any other diffuse lesion, are extremely rare. They may be in the cortex or medulla and vary from the size of a pin's head to that of a nut or even greater, as, for instance, in Bowlby's case, mention of which is made later.

(iv) In old luetic patients a slow sclerotic atrophy of the kidney may be present without any associated specific lesions. On the one hand it may take the form of the arteriosclerosis of the kidney with its atrophic depressions on the surface due

to endarteritis obliterans ; or the type may be pericellular with diffuse extensive change and a general atrophy of the whole organ. The definite proof of a syphilitic origin is not easily got, but as the disease is a cause of sclerosis in other organs, notably the central nervous system, it is justifiable to assume in certain cases with a well-marked history and with other specific lesions that the changes in the kidney are due to this cause.

C. Nephritis in Hereditary Syphilis. The lesions of hereditary syphilis, be they early or late, differ in no particular from those of acquired syphilis. All forms have been observed, but especially the chronic. They have been described as the pale kidney, red atrophic kidney, the amyloid kidney, the sclero-gummatous kidney. There is also a parenchymatous nephritis with amyloid degeneration, which is common. Cassel, in thirty-one infants, the subjects of hereditary syphilis, found albuminuria in six, and in twelve autopsies found renal changes in ten.

Clinical Manifestations. Rare examples of anomalies of urinary secretion have been reported, as, for instance, cerebral syphilis giving rise to diabetes insipidus. Of nine cases of diabetes insipidus reported from Osler's clinique by Fletcher, five had cerebral syphilis.

A. Nephritis in the Secondary Period. The kidney is affected in 3 per cent. of cases of secondary syphilis (Petersen⁴⁶). Symptoms of an affection of the kidney may appear as early as the second month, but any time up to the first two years after the infection. Mauriac⁴⁷ gives four weeks and three years as the limits of the appearance of nephritis of the secondary period. It has been shown that the onset of secondary symptoms is frequently accompanied by albuminuria, but in this condition without other symptoms it does not signify more than the albuminuria seen in other infections. Here the albuminuria may be slight and transient.

When the kidney is more definitely attacked, the onset is often marked ; there are lumbar pains, oedema, fever, digestive disturbances, with anorexia, nausea, and vomiting. The picture is typically that of a nephritis due to cold—in these cases even

cold is often the exciting factor—or to scarlet fever. Often, however, the onset is less severe; there may be no fever, no lumbar pains; it is the oedema on the face, legs, or scrotum which forces itself on the patient's attention; often the oedema is general and intense.

The amount of urine falls to 500 c.c. or thereabouts. Often it contains blood and is smoky. The specific gravity is raised. The remarkable feature, and to some extent a characteristic one, is the presence of enormous quantities of albumin, causing the urine to become solid on boiling. The amount present varies about 15–25 grammes per litre, but it may be as high as 110 grammes (Decouts⁴⁸). The albuminuria may after disappearing slightly reappear in its original amount; this may be coincident with a recrudescence of the secondary rash. Red cells, epithelial cells, leucocytes, and several varieties of tube casts may be seen. The renal permeability to methylene blue is either normal or raised. The increased blood pressure may be absent, and likewise the cardiac hypertrophy and gallop rhythm of the heart.

The course of the disease is like other varieties: if begun early the specific treatment may check the disease. Some cases have been recorded in which a spontaneous cure was effected. In severe cases the patient may succumb to uraemia, to oedema of the lungs or the glottis, to heart-failure or to a superadded infection, as, for instance, erysipelas or broncho-pneumonia. Patients may show amelioration and recrudescence, or the acute may give place to a chronic affection.

The points which distinguish an acute nephritis of syphilitic origin from other forms are: first, that the amount of urine is not lessened to the same extent as in other forms with the same amount of albumin; secondly, that in proportion to the amount of albumin casts are rare; and, thirdly, that the general type of the disease affects the patient as a rule less than the other types.

B. *Nephritis of the Tertiary Period.* An acute type may come on which is similar to that in the secondary period, but difficult to distinguish from an infection superimposed upon a kidney

already having been attacked by the syphilitic poison. Other types are better known :—

(i) *The Amyloid form.* The infection usually has been three to ten years previously, and the patient has had frequent tertiary manifestations in the skin or in the bones. The face is pale yellowish, and he is anaemic ; his general condition is bad, his digestion poor, and he has occasional oedema of the face or of the legs. The urine contains a large amount of albumin, but the amount may be diminished or increased. There is no increased blood pressure : the spleen and liver are large and there may be diarrhoea as evidence of a similar condition in the intestines. Death almost always supervenes from a gradual increase in the cachexia.

(ii) *The form simulating chronic Bright's Disease.* There is nothing specific in the features of this type. There is polyuria, hypertension of the arteries, and the course of the disease is that seen in chronic nephritis, death occurring in the end from uraemia, cerebral haemorrhage, &c. A thorough antisymphilitic medication may temporarily arrest the progress of the lesions.

(iii) A third complex type is seen in those cases in which there is a sclero-gummatous change in the kidney associated with the same condition of the liver. Except for the presence of albumin in the urine the condition of the kidney might give no signs of its presence ; but when a large portion of the kidney substance is interfered with the usual signs of sclerosis of the kidney are manifest, e.g. increased blood pressure, oedema, cachexia, &c.

(iv) *Gummata of the kidney.* They do not usually occur before the fourth or fifth year of the disease (Keyes⁴⁹). They may throughout their course be wholly latent ; if, however, a gumma invades the pelvis, the symptoms are those of a tuberculous lesion. Occasionally a gumma may give rise to sudden attacks of pain similar to that of stone. The following case may be given as an example :—

Charles D., 41, labourer. He had been in the navy for thirteen years and had had syphilis in 1882, Malta fever in 1885,

and influenza some years ago. He had had no rheumatism, cough, or pleurisy, and there was no history of consumption in the family.

For six months he had had sharp pain in the right loin; lately this had become worse and more continuous. They were paroxysmal attacks and came on sometimes when walking, sometimes when stooping; the pain was very severe, never went down the groin, and never made him vomit. He lost twelve pounds in weight. For the previous five days the pain had been referred to the tip of the penis; there had been pain on micturition, and the urine had been thick; for the previous four days the right testicle had been swollen.

He was a healthy-looking, well-developed man. There was marked tenderness in the right loin back and front, and along the line occupied by the ureter; the right vesicula seminalis was enlarged, as was also the body of the right testis, which was very tender; the epididymis on the right side was normal, but the vas deferens was thickened and tender. The urine had a sp. gr. of 1,026, was acid, contained a slight amount of albumin, with a deposit of cells and granular débris. No tubercle bacilli were found on any of several occasions on which they were sought for.

There was slight temperature during the first four days of observation. The testicular swelling gradually disappeared, but the epididymis became swollen for a time, but finally disappeared. The treatment was by potassium iodide, under which all signs and symptoms of the disease disappeared during two months of observation.

Gummata of the kidney are sometimes so large as to give signs of a renal tumour, as in a case reported by Bowlby.⁵⁰ The patient was a woman, aged 40, with swelling of the right renal region. The kidney was large, hard, easily movable, and evidently the seat of a tumour of considerable size. A new-growth was diagnosed and the kidney excised. Its weight was seventeen ounces and the surface was nodular. The organ cut like fibrous tissue and presented the almost cartilaginous consistence of a gummatous testis. The renal tissue had entirely disappeared.

The microscopic examination showed a small-cell infiltration and caseous degeneration. The patient recovered rapidly.

Nephritis of Hereditary Syphilis. Nothing specific is seen in its onset or course—unless it be the association of other lesions of hereditary syphilis, especially liver, spleen, or sense organs. The affection is as a rule a slow chronic nephritis, sometimes latent, sometimes showing acute periods. Iodide medication may delay the course of the disease for a time. Death is usually the only termination of the disease.

Diagnosis and Treatment. Syphilis is a frequent cause of inflammation of the kidney, and therefore should be borne in mind by clinicians when investigating disease of this organ.

The nephritis of the secondary period is, as a rule, not difficult to diagnose, especially if the renal affection occurs as part of the general manifestations. But when an infection is known to have taken place it is not always easy in the absence of other secondary symptoms to attribute the nephritis to the syphilitic virus; under these circumstances the nephritis may be due to an abortive scarlatinal attack, a severe tonsillitis, or even a specific sore throat. Though there is little doubt that actual syphilitic affections of the kidney do occur, yet in the absence of characteristic anatomical changes and pending a re-examination of the affected tissues in the light of recent work on the *Spirochaete pallida*, these questions cannot profitably be further discussed. Again, the possibility of such physical agents as cold and mercurial medication being able to produce a nephritis must be mentioned. Chauffard has reported two cases of syphilitic subjects (in the secondary stage) suffering from acute nephritis as the result of exposure; one was cured at the end of a fifteen-days' milk diet without any medication; the second did not improve at all until at the end of three weeks he was put upon specific treatment. It is possible that in the one case the condition was a nephritis due to cold acting on a kidney weakened by the infection, while the second was one of true syphilitic infection brought on acutely by cold. Mercurial treatment in certain cases may give no improvement whatever, and may even

appear to aggravate the condition ; but, on the other hand, in others it may be well borne and lead to rapid improvement, and if discontinued to a recrudescence of symptoms. The reason appears to be that so great a disturbance of the tissues of the gland has taken place that no amount of treatment directed only against the infective agent can be of service. The same may be noticed in certain lesions of the liver, especially those of acute necrosis. In view of all the difficulties in the way of successful treatment, the recommendations of certain members of the French school are excellent, namely, to treat all suspected cases of secondary syphilitic nephritis on a milk diet for a few days, observing carefully if any diminution in the oedema or quantity of albumin in the urine is effected ; then, if little or no change takes place, to put the patient on mercury, preferably by inunction, beginning by small doses so as to test the tolerance of the patient to the drug. The drug should be continued for several months after a cure has been effected, for the liability to relapses is considerable. In the diagnosis of chronic nephritis or amyloid disease, when the ordinary precursors of nephritis are absent a careful search must be made for any possibly syphilitic cicatrix, especially remembering the liver and spleen. Late hereditary syphilis should not be forgotten ; when suspected a thorough course of iodide may be followed by cure, often in a marvellous way, and even amyloid degeneration may yield to it. The drug should be given in increasingly great doses and may be combined with mercurial treatment. If, however, an old lesion of the kidney interferes with the functions of the organ, specific treatment cannot be expected to restore an irretrievably damaged structure.

Syphilis of the Adrenals. Amyloid changes are not infrequent when the change exists in other organs. Gummata have been described and interstitial changes. Ribadeau-Dumas and Pater⁵¹ have recently made an exhaustive study of the lesions of the adrenals in twenty cases of hereditary syphilis, and they have been struck with the apparent affinity that the spirochaetes possess for this gland. They describe an acute inflammation with exudation of blood cells, areas of necrosis

under the capsule, both showing abundance of spirochaetes. A diffuse sclerosis and an atrophy are also found.

Ureter. The ureter has been seen affected in extremely rare cases. Hadden has described an undoubted case.

Bladder. Syphilitic affections of the bladder are extremely rare. Ulceration has been described from the breaking down of gummata.

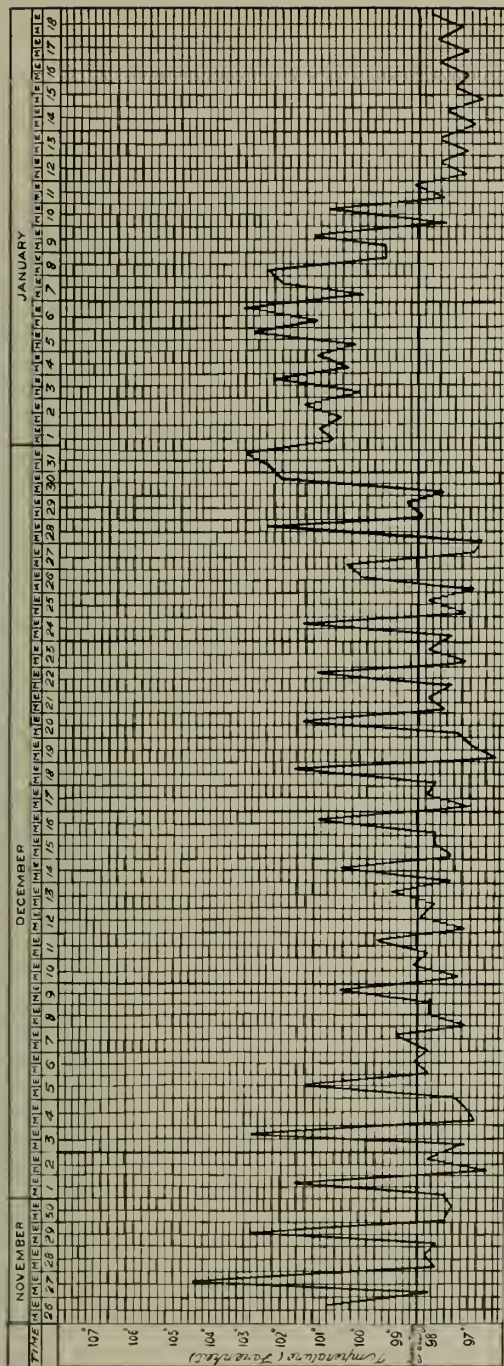
Osler
A. G. Gibson

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47. Mauriac, Arch. gén. de Méd.: Paris, 1886, vol. ii, p. 385
48. Decouts, Thèse de Paris, 1878.
49. Keys, Syphilis: London, 1908.
50. Bowlby, Trans. Path. Soc. Lond., xlviii, p. 128; three cases have been reported by Israel—quoted by Keyes, Syphilis: London, 1908.
51. Ribadeau-Dumas and Pater, abstract in La Semaine Médicale: Paris, 1909, p. 315.

PLATE I



Syphilitic Fever. Simulating Tertian malaria (Phillips).

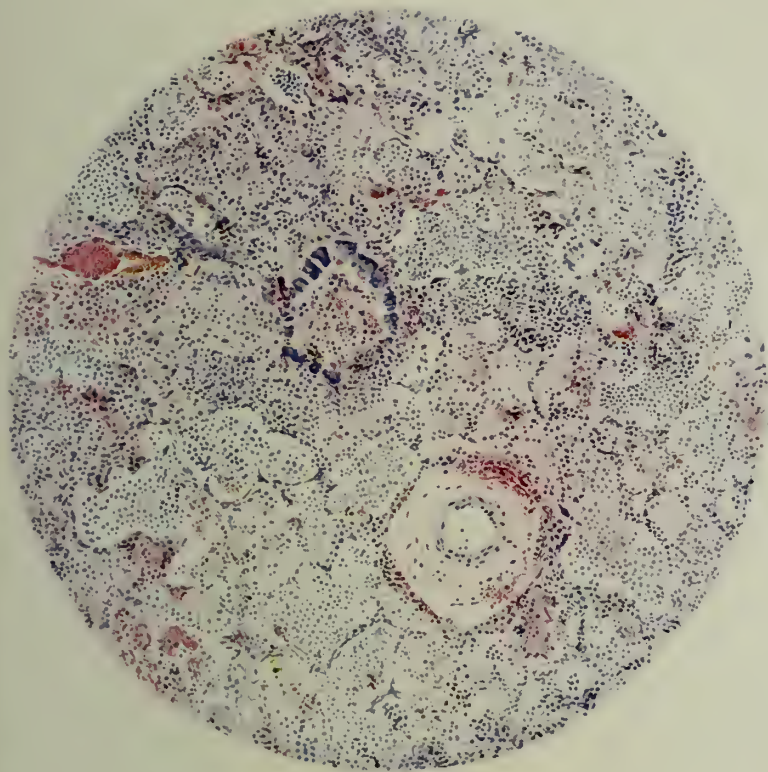


PLATE II.—Section of lung from a case of syphilitic pneumonia (white pneumonia). To the right of the centre and below it is a small pulmonary artery showing periarteritis. To the left of the centre and above is a small bronchus filled with inflammatory cells, and some blood cells. The rest of the section consists of living alveoli filled with cellular exudation and some serous exudation. Stained by hematoxylin and eosin.

PLATE III



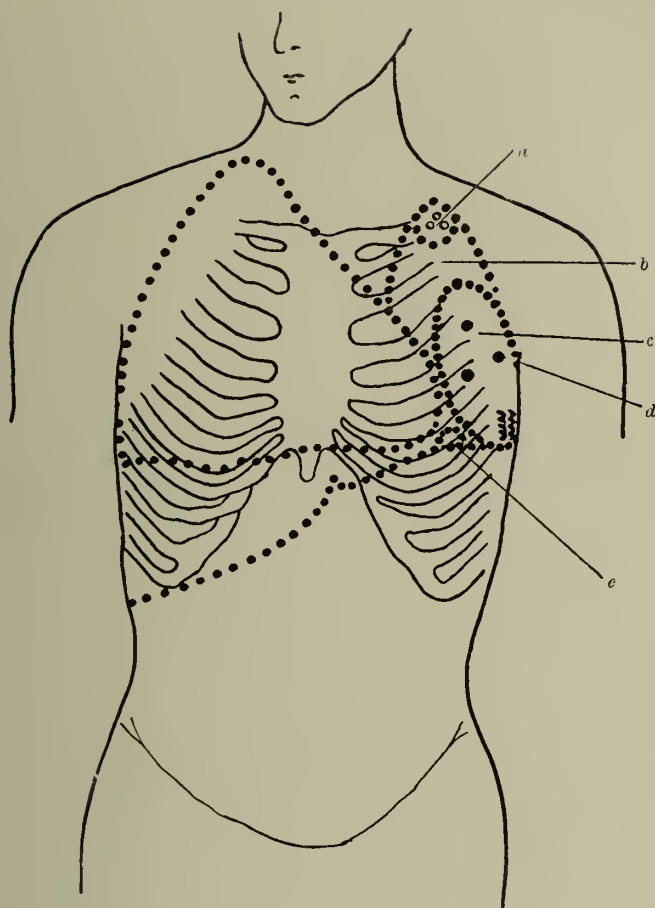
Radiograph of a case of gumma of the lung.
Kindly lent by Dr. R. J. M. Buchanan of Liverpool.

PLATE IV



Radiograph of the same patient after specific treatment.

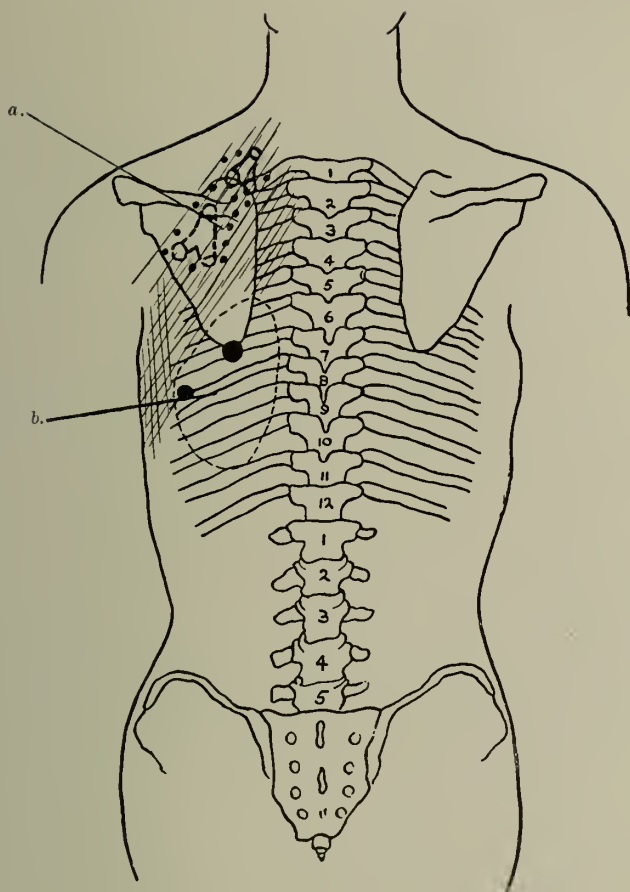
Kindly lent by Dr. R. J. M. Buchanan of Liverpool.



PHTHISIS SYPHILITICA OF 25 YEARS' DURATION

E. W., aged 38, showing the condition of the chest in front: *a.* cavernous breathing and crisp crackles; *b.* boxy percussion note, puerile breathing and a few crepitations; *c.* cardiac dullness; *d.* cardiac impulse, below this was inspiratory friction synchronous with the heart beat; and at *e.* retraction. The right side was typically emphysematous, the left shrunk with diminished expansion.

Kindly lent by Dr. R. J. M. Buchanan.



PHTHISIS SYPHILITICA OF 25 YEARS' DURATION

E. W., aged 38, showing the condition of the chest behind : *a.* tubular breathing, crisp crepitations, diminished percussion note, increased vocal fremitus, resonance and pectoriloquy ; *b.* friction, inspiratory suction, expiratory râles, clucking and quacking sounds. The heart sounds were heard over the oval area indicated.

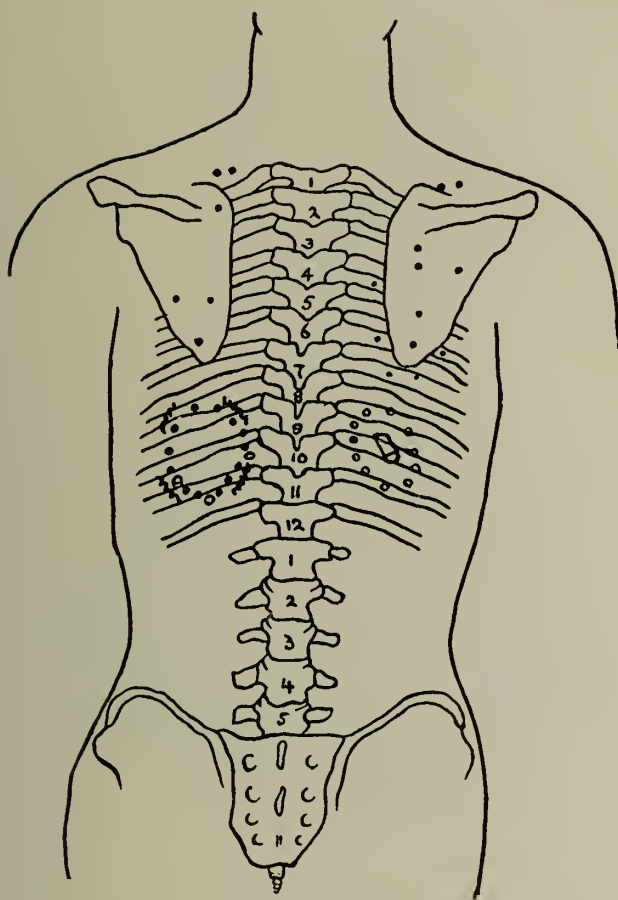
Kindly lent by Dr. R. J. M. Buchanan.

PLATE VII



Radiograph of E.W.'s chest, showing the extreme displacement of the heart shadow to the left, owing to contraction of the left lung. The clear area on both sides of the middle line is due to the hypertrophied right lung.

Kindly lent by Dr. R. J. M. Buchanan.



GUMMA OF LUNG

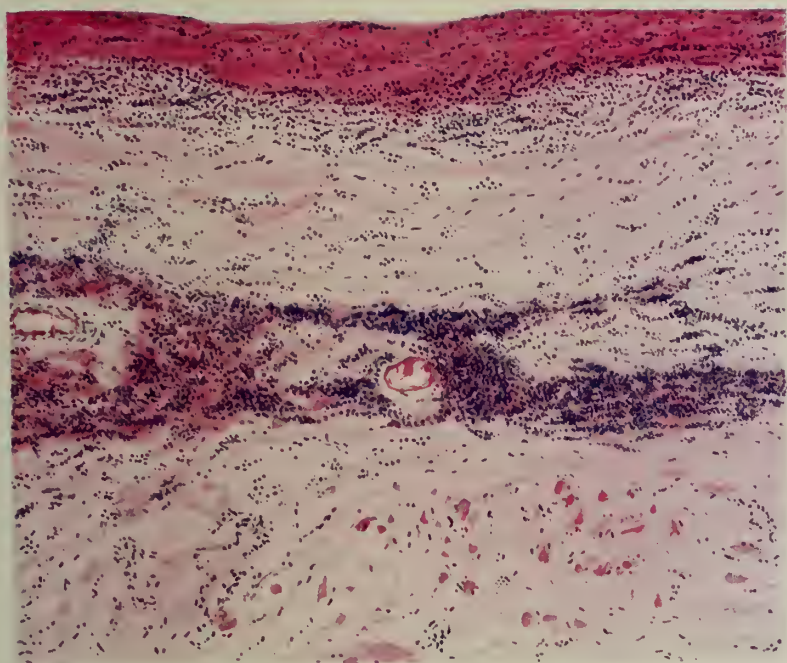
On the left side there was dullness, diminished vocal fremitus and resonance, fine superficial friction, and crepitations with inspiratory suction; on the right there was increased vocal fremitus and resonance, pectoriloquy, harsh inspiration and some dullness, inspiratory crepitations and some sinking in of the chest wall.

Kindly lent by Dr. R. J. M. Buchanan.

PLATE IX

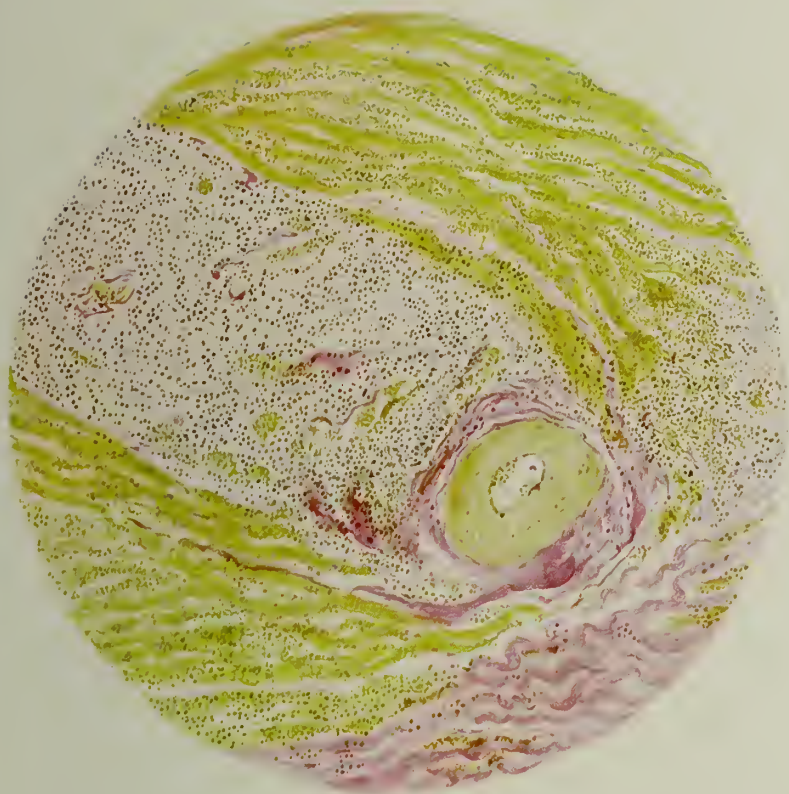


The interior of the left vontricle and aorta from a case of syphilis of the heart (about one-third natural size). There is a gumma of the endocardium at *a*, and a healed gummatous infiltration of the endocardium at *b*. In this case there was a primary left-sided failure followed by right-sided failure.



GUMMATOUS ENDOCARDITIS.

PLATE X.—To show the microscopical features of gummatous endocarditis. The upper layer shows a thickened endocardium infiltrated with inflammatory cells and very deeply stained red from red cells mostly disintegrated. Across the centre is a trabeculated band of intense infiltration with lymphoid cells. Below is the myocardium, infiltrated with connective tissue and showing only a few atrophied muscle cells. Stained by hæmatoxylin and eosin. ($\times 120$.)



GUMMATOUS MYOCARDITIS.

PLATE XI.—To show a gummatous condition of the myocardium, the lower part (red) shows the fibrous tissue newly formed; a vessel is seen whose walls are much thickened, to the left there is considerable infiltration with round cells, both between the muscle fibres (yellow) and elsewhere. Stained by van Gieson's method and hæmatoxylin, by which the fibrous tissue is stained red. ($\times 120$.)

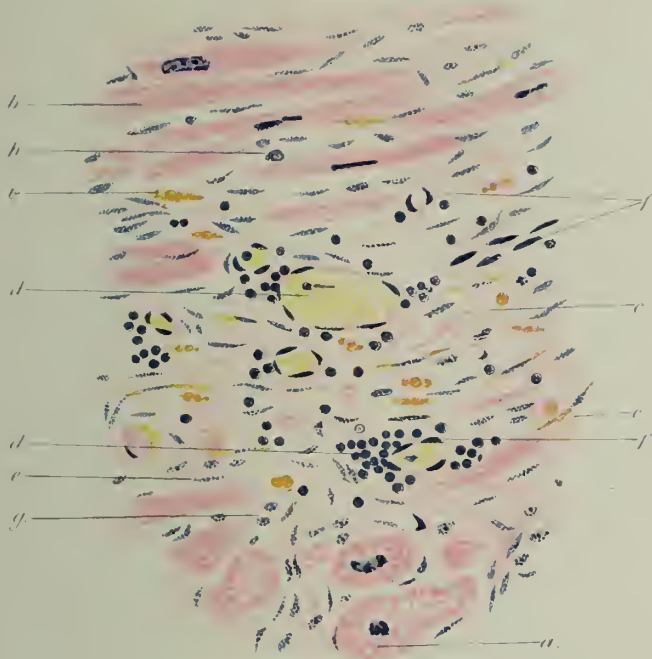
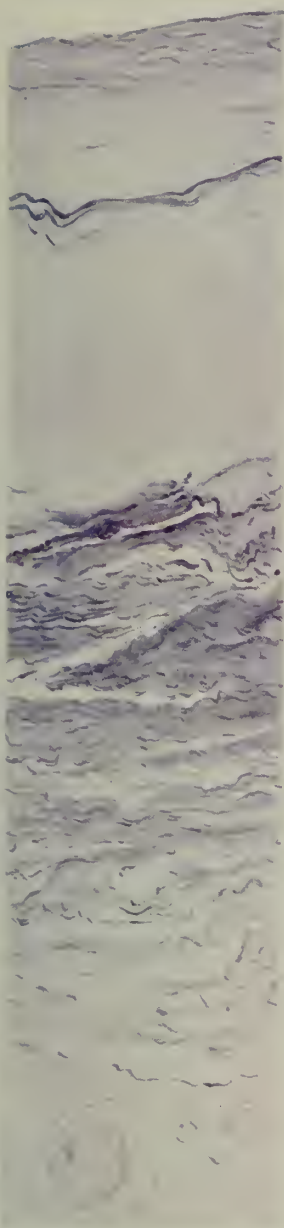


PLATE XII.—Syphilitic interstitial myocarditis. Stained with alum haematein and alcohol eosin. ($\times 200$.)

- a.* Transverse section of muscle fibres.
- b.* Longitudinal section of muscle fibres.
- c.* Wasting muscle fibres.
- d.* Small blood vessel surrounded by small mononuclear cells.
- e.* Fibroblast in new connective tissue between wasted muscle fibres.
- f.* Endothelial cells.
- g.* Plasma cell.
- h.* Mononuclear cell.
- i.* Granules of pigment (?) in atrophied muscle fibres.

(Kindly lent by Professor Sims Woodhead.)

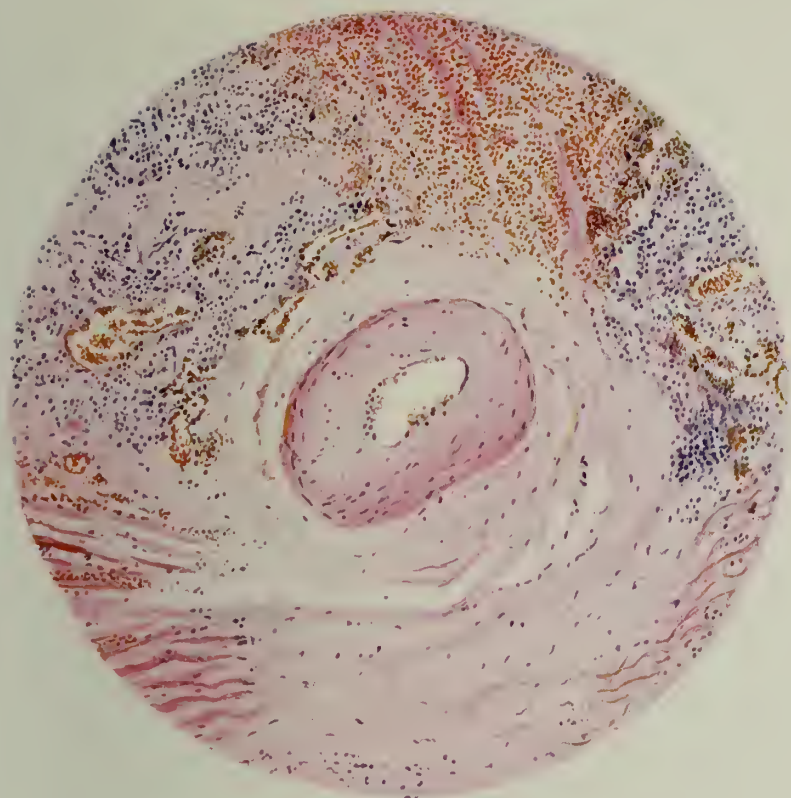


(a)



(b)

PLATE XIII.—Drawings from sections of syphilitic aortitis, (a) stained by Weigert's elastin stain ; (b) stained by hæmatoxylin and eosin. In *a* the intima is very much swollen and shows little elastic tissue, lower down in the main substance of the media the elastic fibres are irregular and interrupted at several spots ; *b* shows the degenerate intima with few cells and the enormous cellular infiltration of both media and adventitia which accompanies the vasa vasorum.



ENDARTERITIS OBLITERANS.

PLATE XV.—Section of a branch of a coronary artery from a case of gummatous myocarditis, to show the condition in endarteritis obliterans. Notice the new formation of blood vessels in the neighbouring parts. The remains of muscle cells are shown on either side below the centre. (Hæmatoxylin and eosin.) ($\times 120$.)

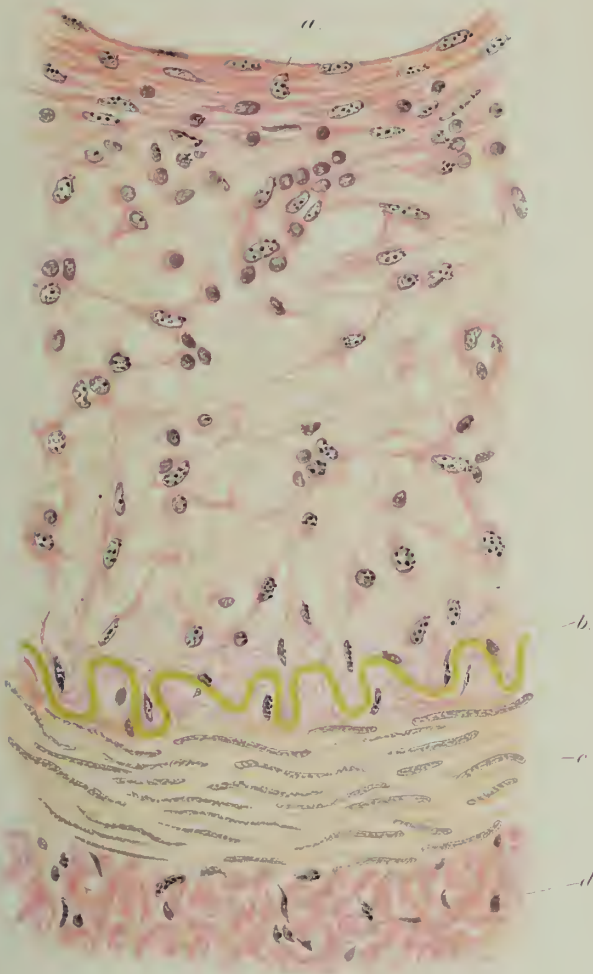
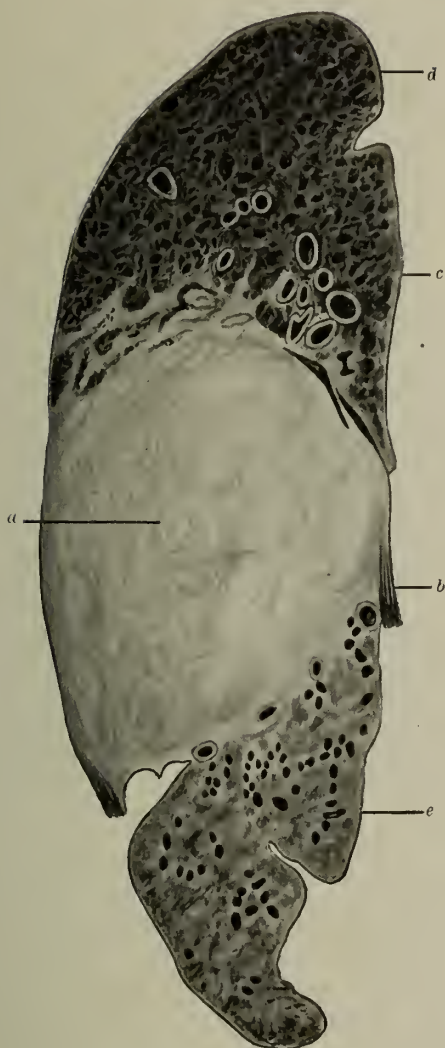


PLATE XVI.—Drawing of small segment of section of a cerebral artery, syphilitic endarteritis obliterans. Stained with alum hæmatein and van Gieson's stain. ($\times 300$.)

- a. Lumen of the vessel bounded by layers of proliferating endothelial cells.
- b. Internal elastic lamina. Note the great similarity of the cells on each side of this membrane. These are probably endothelial cells lining small nutrient blood vessels (*vasa vasorum*).
Between *a* and *b* the intima is enormously thickened. In this thickened intima fibroblasts and mast cells may be seen in considerable numbers. Sections of small blood vessels (not usually present in the tunica intima) are well seen. These are lined with well-defined endothelial cells.
- c. Muscular coat.
- d. Adventitia.

(Kindly lent by Professor Sims Woodhead.)

PLATE XVII



A large gumma occupying the greater part of a vertical section of the liver (after Rolleston). *a*. Fibro-gummatous mass; *b*. diaphragm; *c*. lower lobe of lung; *d*. upper lobe of lung; *e*. anterior part of right lobe of liver.

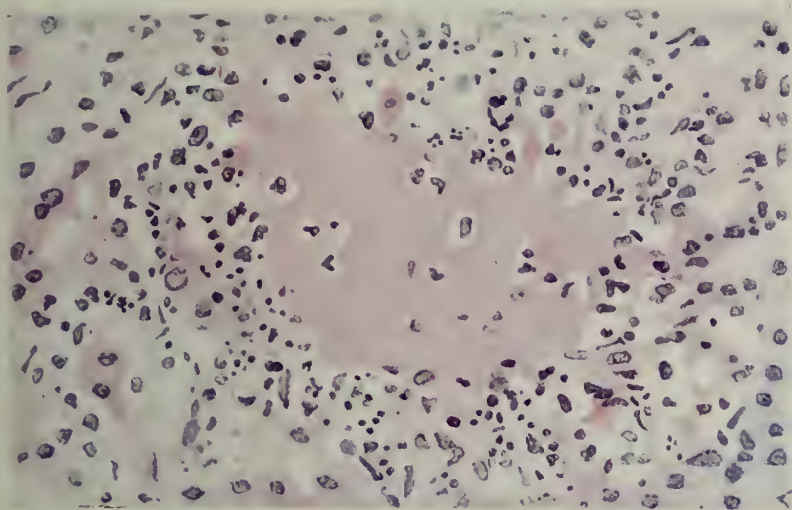


PLATE XVIII.—A “miliary” gumma from a case of congenital syphilitic hepatitis. The liver showed the common pericellular hepatitis, the isolated liver cells are shown in the periphery of the drawing. Stained by hæmatoxylin and eosin. ($\times 350$.)

PLATE XIX



Botryoid liver, from cicatrization, due to gummata.

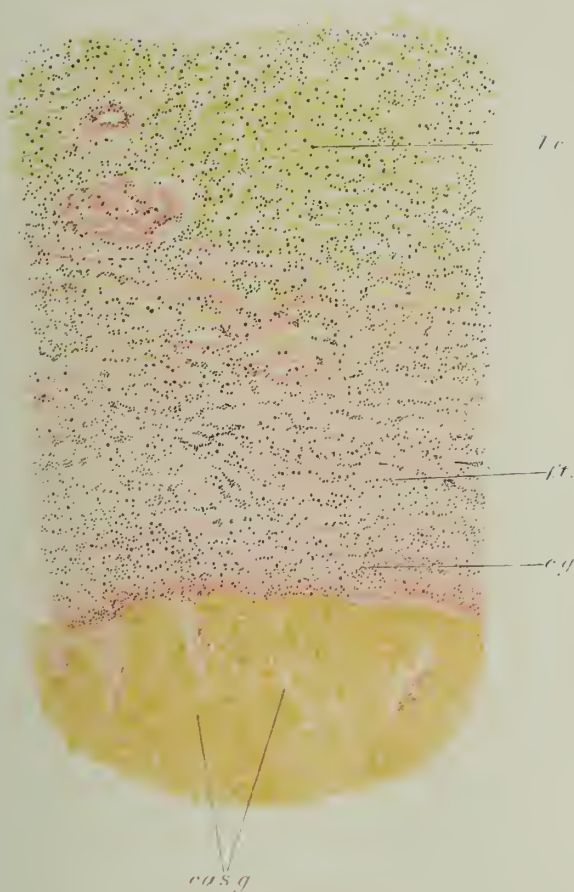


PLATE XX.—Drawing from a section of liver with hepatitis gummosa.
Stained with alum hæmatein and van Gieson's stain. ($\times 20$.)

f.t. Continuation of the fibrous tissue from the capsule around the caseous mass into the substance of the liver, in which are numerous sections of embryonic vessels, etc.

l.c. Small patches of liver tissue left between the bands of fibrous tissue.

c.g. Fibrous external zone; and (*cas. g.*) caseating central zone of softening gumma just below the capsule.

(Kindly lent by Professor Sims Woodhead.)



PLATE XXI.—Drawing from a section of syphilitic cirrhotic liver.
Stained with alum hæmatein and picro-erythrosin. ($\times 50$.)

- p.s.* Increase of fibrous tissue in portal spaces. This increase of fibrous tissue is seen to extend from the space for some considerable distance into the lobules; the columns of liver cells (*l.c.*) are more atrophied at the margin than at the centre of the lobule (*l.c.¹*).
- c.t.* Nucleated fibrillated tissue between the atrophied liver cells.
- a.* Bile duct.
- p.v.* Portal vein.

(Kindly lent by Professor Sims Woodhead.)

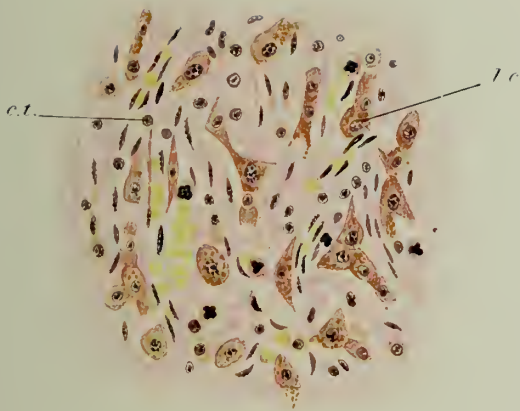


PLATE XXII.—Drawing from a section of syphilitic cirrhotic liver.
Stained with alum hæmatein and picro-erythrosin. ($\times 300$.)

l.c. Small masses of granular and somewhat atrophied liver cells,
between which is an increased amount of nucleated fibrillated
connective tissue (*c.t.*).

(*Kindly lent by Professor Sims Woodhead.*)



Gumma of the liver with enlargement (Walter R. Y.).

PLATE XXIV



Congenital syphilis of the liver with gummata. The limits of the enlarged spleen are also seen.

THE CLINICAL ASPECTS OF GENERAL PARALYSIS

BY

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CHAPTER VIII

GENERAL CONSIDERATIONS

GENERAL Paralysis is the most distinct variety of insanity, and is one of the most fell diseases that afflicts the human race. It differs from most other varieties of insanity in having an assignable cause, in running a definite course, in having a pathognomonic morbid anatomy, and in its association with characteristic bodily symptoms.

The class of the population on which it is mainly incident has long been discerned, but only of very late years has its peculiar distribution been accounted for. It is in the main a disease of middle life, and most often of the male sex. It usually affects vigorous, energetic, successful men, who have lived full, active, busy lives in cities; who are married; who have indulged freely in eating and drinking, and in sexuality; and in whom an hereditary disposition to insanity is absent. Of occupations, the army furnishes by far the most examples, and the priesthood the fewest. Among Roman Catholic priests it is almost unknown. While this is the rule, there are exceptions. It does occur in women, but in much fewer women than men. It does occur in persons of insane parentage. It does occur occasionally in children, and in the old. It does occur occasionally in agricultural districts. It does very rarely occur in Roman Catholic priests.

Such a distribution is evidently significant. It means something. It gives a clue to the causation of the disease, but a clue that was never followed successfully. Not until it was found that all cases of juvenile and adolescent general paralysis occurred in the subjects of congenital syphilis, did the meaning of the peculiar distribution become manifest. Then syphilis was searched for in other cases of general paralysis; and, when searched for, it was found. It was found to have existed in

general paralytics in as large a proportion of cases as in any manifestation of unquestionably syphilitic disease. It was found to have preceded general paralysis in about 80 per cent. of cases ; and, in other diseases that are unquestionably syphilitic, there is a residue of 20 per cent. in which no history of syphilis and no other stigma of syphilis can be found.

Now the peculiar distribution of the disease became clear. The classes of persons who are most liable to general paralysis are those that are most liable to syphilis. The classes that are most exempt from general paralysis are those that are least likely to contract syphilis. With this knowledge in our minds we can understand why general paralysis is more frequent in men than in women, and yet why some women are affected by the disease. We can understand why it is more rife in towns and in the army, and why it should yet sometimes appear in the country and among civilians. We can see why the priesthood is so nearly exempt. We can see why the active, vigorous man, prone to fast living and sexuality, is more liable than the man whose character is the reverse. The distribution of general paralysis is the distribution of syphilis.

Syphilis is therefore by far the most important factor in the disease ; but it is not the sole factor, for but a very small proportion, estimated at 2 per cent., of those who contract syphilis become general paralytics. There must be some factor, present in this 2 per cent. and absent in the other 98 per cent., which determines the existence of the disease. Since general paralysis sometimes occurs in persons from whose history syphilis seems to be excluded, it seems as if this second factor might, in a very small number of cases, be of itself sufficient, without a syphilitic basis to act on. It would be rash, however, to draw any such conclusion ; for, since the syphilitic origin of general paralysis has been deduced, the percentage of cases in which a history of syphilis could not be found has constantly diminished, and, while cases in which no history of syphilis and no stigmata of syphilis can be found are not at all infrequent, cases in which syphilis can be positively excluded must be extremely rare. Syphilis may be contracted in very many ways besides that

of sexual intercourse. It is often contracted unknowingly. Secondary symptoms are sometimes so slight as to attract no notice and demand no relief.

Some other factor besides syphilis is necessary, however, to produce general paralysis, for, as already noted, only a small percentage of syphilitics become general paralytics, and in China and Japan, where syphilis is extremely common, general paralysis is rare. What this factor is, is not ascertained with certainty, but it is almost certain that there is more than one factor additional to syphilis. Since general paralysis is practically the same disease as *tabes dorsalis*, but beginning in a different region of the cerebro-spinal axis, the knowledge of *tabes* may help us. Now, cases of *tabes* have been observed in which the upper extremities have been first and most affected, and these have occurred in persons who have used their arms excessively. May it not be therefore that the incidence of the disease on the brain rather than on the cord is due to the fact that the brain has been used to excess—has at any rate been used more in proportion than the limbs? The facts of the distribution of the disease make this at least plausible, for, long before the syphilitic origin of either *tabes* or general paralysis was suspected, it was noted that general paralysis seemed to prefer active, energetic, strenuous, successful, busy men. It affected, that is to say, those who used their brains much, just as brachial *tabes* affects him who has used his arms much.

Cases have, moreover, been recorded, in which several general paralytics have derived their syphilis from the same source; and this has led Dr. Mott to suggest (see vol. iv) that there may be a special variety of the spirochaete of syphilis, having a peculiar power of producing general paralysis rather than any other late manifestation of syphilis. The facts certainly appear to favour this view.

Lastly, Dr. Forbes Robertson claims to have identified certain bacilli as the immediate cause of general paralysis, a cause which acts more readily in a syphilized soil, but which is quite capable of acting in the absence of syphilis if other favouring conditions are present. With these bacilli he claims to have produced in

lower animals symptoms closely resembling general paralysis ; and, with a serum prepared by means of these bacilli, he claims to have improved or cured general paralysis. The bacilli are found in the mucosa of the nose and throat, and are believed by Dr. Robertson to make their way up the lymphatics to the brain, having been found there, and in the intermediate positions. Dr. Forbes Robertson is known to be a most able and painstaking observer, but his conclusions have not yet been endorsed by workers in any other laboratory, and our attitude towards them must for the present remain one of suspense.

General paralysis has in some cases followed, at no distant interval, a blow on the head ; in others, an attack of influenza ; in others, a period of great anxiety or grief ; in others, again, a time of very strenuous mental exertion ; and it seems that, while the lesion cannot occur except in a person the subject of syphilis, it needs a provocative and localizing factor to determine its occurrence, and its incidence on that part of the nervous system which actuates conduct and underlies the processes of mind. The influence which is most powerful as this second factor seems to be excessive, or at least high, physiological activity of that part of the brain that is primarily attacked ; and hence an additional reason, besides the greater prevalence of syphilis therein, for the greater frequency of syphilis in cities ; for the special liability of vigorous, active, and successful men ; and for the smaller liability of Oriental races, whose members, though much subject to syphilis, are fatalistic, and less susceptible to anxiety, worry, and depressing emotions than Occidental races.

General paralysis is called a progressive disease ; and, in the sense that the great majority of cases run a downward course, and end fatally, it is progressive ; but it is in no case continuously or uniformly progressive. Its course is always remittent, and not infrequently, in the early stage, intermittent. In typical cases, and especially in younger men, the remittance follows a definite course. The disease is marked by periodical crises, occurring at intervals which become shorter as it progresses, and, while always of the same character in the same case, vary

much in different cases. The most usual form that the crisis takes is that of universal convulsion, indistinguishable from that of ordinary epilepsy ; but other crises of very different character occur in other cases, the only feature common to all forms of crisis being that they are all of the nature of a nervous discharge—a sudden and excessive liberation of energy from some region of nerve tissue. Instead of the generalized convulsion of ordinary epilepsy, there may be attacks of *petit mal*, followed, in rare cases, by post-epileptic automatism ; or there may be attacks of Jacksonian epilepsy, the convulsion beginning locally in the thumb and fingers, or in the eyes or lips, and gradually spreading till it attains universality ; or there may be ‘apoplectiform’ attacks, in which the patient loses consciousness and becomes generally paralysed without perceptible, or without conspicuous, convulsion. Or the crises may be of the nature of sudden rises of temperature with flushed face and moist skin ; or they may take the form of vomiting and diarrhoea ; or there may be a simple subsidence into lethargy, stupidity, and semi-coma, lasting a few hours. Whatever the form the crisis takes, some form of recurring crisis takes place in every case of general paralysis, and, as already stated, the crises are always the same in form in the same case, and tend to occur more frequently as the disease advances.

The occurrence of the crises has a very conspicuous influence on the course of the disease. Immediately after each crisis the patient is much worse than he was before it, and thereafter he gradually improves, but he never improves up to the point at which he was before the occurrence of the crisis, for, before he has reached this point, another crisis takes place ; and, on emerging from it, he is found to be worse than he was immediately after the previous crisis. The course of the disease is one of sudden plunges, each deeper than the last, each followed by a gradual recovery that is less complete than the recovery from the previous plunge. This is the typical course of the disease, but the sequence of events here described is often obscured and interfered with by various causes, and presents many variations.

It is manifest that if the occurrence of a crisis were, for any

reason, to be postponed sufficiently long, and if the improvement that occurs after a crisis were to continue unchecked, there might be a recovery to a very high standard, a recovery that would be for practical purposes complete, and would constitute an intermission rather than a remission of the disease; and further, that if, after such an improvement, the crisis failed to recur, the disease would be arrested, and we should be in presence of a recovery. Now, it has been already said that at the commencement of the disease the crises are far asunder, and the intervals that separate them become shorter and shorter as the disease progresses. It is at the commencement of the disease, therefore, that we should look for complete intermission, or for permanent recovery, if these are to occur at all; and it is a familiar fact in the history of general paralysis that, after the first attack or outbreak of the disease, there usually follows a period of considerable improvement, which not infrequently amounts to a complete intermission of the disease, lasting for weeks, months, or years. As the persistence of the disease leads to structural deterioration of the brain, it is not to be expected that in the later stages of the disease, even should the recurrence of a crisis be indefinitely postponed, any such complete recovery should take place; nevertheless, in rare instances, even at an advanced stage of the disease, a very surprising degree of amelioration may be attained, and may be lasting.

The explanation of the peculiar course of the disease which has been described must for the present be purely hypothetical, but a plausible hypothesis may easily be constructed. That the disease is essentially syphilitic, is the opinion of the great majority of observers. It is the opinion that at present holds the field, and until Dr. Forbes Robertson's hypothesis receives further corroboration, the syphilitic nature of general paralysis must be regarded as the working hypothesis. Whichever hypothesis we adopt, it is necessary to suppose that the destruction of the nerve elements is due to the action of a poison conveyed to them by the blood, and among the facts of neuropathology few are better established than the power of a poison to produce convulsion, and to act selectively upon some special region of

nerve tissue. The action of strychnine is a case in point. The dependence of the crises of general paralysis, no less than those of the organic lesions of the disease, upon the action of a toxin upon the nerve tissue, may be regarded as settled. The difficulty of explanation begins when we try to account for the periodicity of the crises, and the gradual improvement that takes place between one crisis and the next.

Two explanations are possible. Either the poison is poured into the blood in intermittent gushes, corresponding with the times of the crises ; or it is supplied continuously, but does not produce its critical effect until it reaches a certain saturation point, or until the resistance of the body to its action gives way suddenly after a long and equal struggle.

The first hypothesis is the most obvious, and perhaps for that very reason is to be regarded with suspicion. The production of convulsion, of confusion, of coma, of gastric disturbance and so forth, directly by and upon the introduction of a poison into the blood, is a familiar sequence, and the subsequent gradual improvement of the patient by the elimination of the poison is among the common incidents of disease, and is exemplified in every case of drunkenness ; but in all such cases the poison is introduced from without, and is not elaborated within the body itself. If the poison is elaborated within the body, it is difficult to understand how and where it is accumulated in the intervals between the successive gushes of liberation, and what is the barrier against continual leakage. On the other hand, there is a circumstance which lends plausibility to the supposition that the poison is elaborated in some recess of the body difficult of access by the circulation, for both tabes and general paralysis are wholly unaffected by ordinary antisypilitic remedies, which are so efficacious in the earlier stages of this specific disease. If the toxin is the result of syphilis, then it seems as if it must be secreted by the organism of syphilis, or by tissues affected by the poison of that organism. At any rate, it is difficult to regard the malady as syphilitic unless the living spirochaete takes a part in its production. But if the living spirochaete is indeed responsible, the readiest explanation of the inefficacy of

those remedies that are noxious or fatal to the spirochaete is the supposition that the organism is encapsuled or secluded in some way that renders it inaccessible to the blood containing this remedy. Another explanation would be that those organisms only which are proof against the action of these remedies survive the early treatment of the disease and remain to produce tabes and general paralysis in later life. This may be the character, or a concomitant character, of that special neurotoxic spirochaete which Dr. Mott supposes to be the cause of general paralysis.

This survival of the most resistant of the noxious organisms would fit in better with the second hypothesis—that of the continuous production and issue into the blood-stream of the poison, which cannot, however, produce its critical effect until it has reached a certain degree of concentration in the blood, or until, by its continual action on the resisting tissues, it wears out their resistance, which then suddenly gives way and allows the critical effect to take place. Such an hypothesis, and especially the latter, is consonant with the course of other critical events, occurring in consequence of the production of other internally produced toxins. It would be on all fours with what may be supposed to be the mode of production of a rigor at the invasion of specific fevers; but, on the other hand, it is more difficult on this hypothesis than on the former to account for the gradual improvement that follows on each critical event. If the poison is poured out at intermittent intervals, it is easy to understand that a subsequent gradual elimination or destruction of the poison should be attended by continuous improvement; but if the poison is continuously accumulating in the blood in the intervals between the crises, it is less easy to account for concomitant improvement of the symptoms.

It is a fact, the significance of which is not yet clear, that the crises may be mitigated in severity, and even wholly averted, by measures for the disinfection of the intestinal tract.

CHAPTER IX

CLINICAL COURSE

OUR knowledge does not at present allow us to select decisively between the several alternatives that have been proposed, but this statement of them may serve to suggest the direction that investigation should follow in order to determine a very important element in the nature and course of the disease.

The clinical course of general paralysis is usually divided into four stages, and the division has some convenience, though the stages are arbitrary and not often very distinct. This is especially true³⁷ of the first or prodromal stage, in which the disease is seldom recognized, and often not even suspected. It is very important to remember that the remittent character, which has already been described as characteristic of the disease, prevails throughout all its stages, and in the early period of the disease passes into complete intermittence. The periodicity of the remission is extremely variable in different cases; and, in the same case, is not the same at all its stages. As already stated, the intervals between the crises usually diminish as the disease progresses, but before the actual crises are established the gravity of the symptoms fluctuates, and there may be complete remissions of longer or shorter duration, lasting, in different cases, from a few hours or days to many months, and even years, and separated by intervals similarly unequal. This feature of the early stages of the disease is important to remember for several reasons. It may obscure the diagnosis; it may materially influence the treatment; and it may give rise to legal questions of great importance.

No definite duration can be assigned to the prodromal stage of general paralysis. It is not usually recognized that such

a stage has existed until the disease is become unmistakable, and then it is remembered that for weeks or months previously the patient has displayed aberrations of conduct similar in kind to, but much slighter in degree than, those by which the disease is at length recognized ; and in addition he may have had other symptoms which do not pertain to the established disease. By the time the symptoms are sufficiently pronounced to enable us to say with certainty that the patient is suffering from general paralysis, the prodromal stage is past ; and the utmost that can be inferred from the prodromal symptoms is a suspicion or a likelihood that general paralysis may follow.

The most frequent of the early signs of general paralysis is a change and degradation in the character, conduct, and mode of life. The activity of the patient is increased, but it is carried on at a lower level. He works longer hours, and does more work, but his work is neither so capable nor so fruitful. He loses the grip on his affairs. He loses the sense of proportion, and devotes disproportionate time, energy, and attention to affairs of little moment, while neglecting comparatively, or altogether, those of the first importance. The business man usually becomes less cautious in his business operations. He takes unwonted risks ; he becomes more speculative ; his transactions become more numerous and diverse, and extend to matters outside of his usual range ; they are more daring and more complicated. As might be expected, transactions of such a nature, carried on by a man the keen edge of whose intellect is blunted, are commonly unsuccessful, and the prodromal stage of general paralysis is a time when fortunes are impaired and businesses damaged. But this result does not always ensue. The similarity of the symptoms of general paralysis to those of drunkenness has often been remarked, and it extends to that sharpening of wits and increased brilliancy of intelligence which is sometimes witnessed in the early stages of both. I have known several cases in which fortunes have been made by patients in the early and unrecognized stage of general paralysis ; and in one of these the patient invested large sums in pictures and other works of art, which

realized, at his death, prices in advance of those he had paid for them.

The increased energy of the early general paralytic shows itself not only in the increased number and magnitude of his business transactions. It is exhibited in every part of his conduct. He sleeps less, and eats and drinks more. He reacts more vigorously to every stimulus. Letters that demand no reply are yet answered at length. Letters that might be answered in course of post are answered by telegram. Small pretexts suffice as an excuse for journeys, correspondence, appointments, interviews. His social no less than his business engagements increase. He entertains more ; he shows more inclination for society ; and when in society he takes a more prominent part. He talks more, more loudly, more imperiously, and more egotistically. He becomes lavish. He raises wages, and gives presents, and scatters tips. He associates familiarly with his social inferiors. He is apt to become loose in his sexual relations. He is often irascible and excitable. Combined with these mental characters there is usually an elation, a buoyancy of mind and high spirits, unusual to the subject of them, and beyond what his circumstances warrant. In fact he resembles in every respect a man who is slightly under the influence of drink ; and as, among his other changes of demeanour, he does, even if previously a sober man, drink a good deal, his peculiarities are often put down to the fact that he has ' taken to drink '. Such are the prodromata of one class of cases of general paralysis ; but it is manifest that such conduct is in no way different, except in degree, from that of the fully developed disease, and it is only because the disease is not sufficiently pronounced to be recognized, that these manifestations are looked on as prodromata rather than as symptoms of the developed disease.

Another set of prodromata occurs at the outset of another type of the disease. In this case the patient droops in ability and in activity ; he finds his work a burden to him ; he makes mistakes ; he forgets things. He forgets what he has to do, and he forgets names even that he is familiar with, and uses

frequently. Unlike the case previously described, he recognizes that there is something the matter with him, and he seeks advice, sometimes for the failing memory, sometimes for the headache, which is apt to be severe and persistent. He is dull and apathetic ; gives up his amusements ; sits at home with his head in his hands, and must be roused to make any exertion. He complains that his mind is confused, and often becomes irritable, and breaks out into temper and even violence. The headache, in the early stage of this type of general paralysis, is, as has been said, often severe and persistent ; and as headache is very unusual in most forms of unsoundness of mind, its occurrence in these cases is apt to mislead. It is sometimes so severe as to suggest cerebral tumour, and, not infrequently, it is the trouble for which advice is sought ; and it is not until the patient or his friends are questioned that the presence of other symptoms is elicited. The headache differs from migrainous headaches, which are worst in the morning, and from headaches of ocular origin, which are often worst towards evening, in observing no time or season. It is persistent and continuous, dull in character, and diffused in locality.

Besides the foregoing symptoms, others of more localised character may occur in the prodromal stage of any type of the disease. There may be transient paresis. A limb may become weak, a leg may be dragged, or an eyelid may droop ; there may be transient aphasia, or transient strabismus, which, with a history of syphilis, may give rise to a suspicion of gumma. There may be unaccountable attacks of giddiness, of fainting or vomiting. Sometimes a rise of temperature, nocturnal or continuous, of a degree or two, may precede the definite establishment of general paralysis. Or there may be transient blindness, or deafness, or numbness, or anaesthesia, or even neuralgia. The nervous symptoms that occur in the prodromal stage of general paralysis are, as will be seen from this list, very multi-form in character, but they agree in one feature. They are all transient in duration. Any of such transient symptoms of nervous disease, occurring in a man between 35 and 50, should

bring general paralysis into the field as a possible explanation. Of course, they are common to many other maladies, especially those of syphilitic origin, and a history of syphilis carries, therefore, no weight either for or against the hypothesis ; but, in such cases, the possibility of general paralysis should be present to the mind of the physician.

In some cases, general paralysis is engrafted on tabes, and in such cases the tabes may, in one sense, be regarded as a prodroma of the general paralysis ; but this is rather a forced proceeding. In addition to those cases of tabes on which general paralysis follows, there are a certain number that exhibit infirmities of temper and a want of mental balance, that seem to show that the brain does not remain altogether unaffected by the disease that bears with special incidence on the cord ; and although these mental affections are not at all characteristic of general paralysis, neither does the spinal cord disease, which occurs in the later stages of general paralysis, in any way simulate tabes.

As already hinted at, general paralysis does not display the same symptoms in all cases. In all cases there is a physical disease running a more or less definite course, and accompanied by progressive mental deterioration ; but in this, as in other cases of mental deterioration, the signs of deterioration vary. It is not sufficiently appreciated that the primary and essential feature in every case of mental disorder is negative. It is loss ; it is defect ; it is the removal of ability, of competence, of efficiency, of power of mind, and adaptability in conduct. Whatever else there may be, there is always this negative factor, which is the central and necessary feature in the disorder. It may be that this negative factor stands alone,—that no positive factor is superadded to it, and then the mental character of general paralysis is a gradually increasing dementalization. Beginning with the trifling confusion and forgetfulness that have already been described as prodromata, the loss of mind and conduct gradually progresses until nothing remains. Not the simplest reactions betray the existence of consciousness ; not

the simplest act exhibits a rudiment of conduct. But this simple progression of mental impairment is not invariable in general paralysis, any more than in other forms of mental disorder. It is usually overlaid and obscured by positive symptoms, some of which are, without doubt, due to the overaction of lower regions which have been released from control by the destruction of the regions superior to them; while others are, with our present knowledge, inexplicable. The symptoms due to loss of control of higher centres or regions are, of course, excessive action of lower centres—of centres which are relatively of low level, but yet may be very elevated in the hierarchy, though they are not the highest. Such excessive action of uncontrolled centres produces conduct that is lacking in control, conduct that may be generically termed maniacal, although when it is on a high level, and is not greatly excessive, it is sufficiently described as ‘excited’, while, when it is on a lower level, and is greatly excessive, it merits the specific title of ‘mania’. The other positive symptoms are disorders of mind, which are of two kinds—delusion, and alteration of the affective attitude, that is to say, of the feeling of well-being.

The alteration of the feeling of well-being may be in the direction of increase or of decrease, and at present we are wholly ignorant why some general paralytics experience a vast increase of well-being, and are buoyant, jovial, and happy beyond their powers of expression, while others are depressed and miserable; nor have we any explanation of the fact that the misery is never as great as is the exaltation. There is no other mental disorder in which the exaltation is so great, and the feeling of happiness and general well-being so exaggerated, as it is in some cases of general paralysis; but there are many cases of melancholy in which the depression reaches a far greater depth of misery than is expressed by any case of general paralysis.

The delusions of general paralysis follow the rule observed by delusions in all other cases of mental disorder, in being consonant with the state of affective feeling. When the general pleasurable feeling is exaggerated, then the delusions are of

increased consequence and reputation, increased worthiness, increased capability and power, and increased wealth. When the general pleasurable feeling is replaced by one of misery, then the delusions are of diminished consequence and reputation, of unworthiness, of diminished capability and power, and of poverty. They are delusions of sin and crime, delusions of impotence and incapability, delusions of the unfavourable action of others upon the patient. To whichever class the delusions belong, they are characterized by their enormous and hyperbolical exaggeration. There are other disorders of the mind in which so-called megalomania is evinced, but none in which the delusions are so utterly outrageous in the magnitude of their conception as in some cases of general paralysis; and this character of immensity is apparent in the delusions of the depressed as well as in those of the exalted.

The physical signs of general paralysis are virtually the same in all cases, allowance being made for differences of duration, and for differences in the nature of the periodical crises, as already indicated.

The very earliest sign is usually an alteration of the knee-jerks. This is usually in the direction of exaggeration, the response being slightly or greatly excessive in traverse, but less excessive in rapidity, the return of the limb to its position of rest being usually slow—decidedly slower than the initial excursion. The responses of the two legs are often unequal, and one may even be diminished while the other is increased. In some non-tabetic, and in all tabetic cases, both knee-jerks are greatly diminished or altogether lost.

While the alteration of the knee-jerks is usually a very early symptom, there are cases in which it is not observed until later in the disease, and, of course, when general paralysis is engrafted on tabes, loss of knee-jerks counts for nothing as a symptom of the former disease. In no case, moreover, can alteration of knee-jerks be relied upon, even when combined with mental disorder, to establish the existence of general paralysis. At most it can but justify grave suspicion.

It is otherwise with the pupillary changes. When the characteristic pupillary change is certainly present, and is associated with mental disorder of whatever kind, then the diagnosis of general paralysis may be safely made. The difficulty is to be sure, when the pupillary affection is but slight, that it is present at all. The earliest of the pupillary signs is the sluggish contraction of the pupil when exposed to light. When a bright flare is suddenly cast upon the eye, the pupil should contract immediately and rapidly : in the pupillary affection of general paralysis it contracts after an interval, slowly, less completely than it normally would, or perhaps it fails to contract at all. If one eye is shaded, and a bright light is thrown on the other, the pupil of the shaded eye should contract. In general paralysis this consensual contraction is slight, or is absent. When the axes of the eyes converge, and accommodation is adjusted to a near object, the pupils contract with some proportionate relation to the degree of convergence. In general paralysis, at any rate in its later stages, the accommodative contraction is diminished or lost. Lastly, when the skin of the neck is pinched or the hair on the temple is pulled, the pupil normally dilates ; but in general paralysis this reflex may be absent. These reflexes are affected usually in the order in which they have been here enumerated ; though the consensual reflex is sometimes the first to be lost. The loss of the accommodative reflex is always later than that of the reflex to light ; and may be postponed to a late stage of the disease.

In addition to these changes in the reflexes, the pupils may be contracted to the size of pins' heads at quite an early stage of the disease, and so remain for months or years, no further contraction being obtainable by any exposure to light. Towards the termination of the disease the sphincter relaxes, and the pupils regain their normal size and often greatly exceed it. In the early stage the pupils are sometimes unequal, but in making this observation care must be taken that both eyes are exposed to the same brightness of light. The consensual contraction ensures approximate equality, but not complete equality. More-

over, some inequality is not infrequently met with in the normal, and inequality often appears to be present in persons whose pupils are very mobile. When affected by general paralysis the pupils are not very mobile.

General paralysis of the insane being a disease affecting the musculature, attended by mental disorder, it is never safe to make an affirmative diagnosis unless there is a combination of mental disorder with one of the motor symptoms here described ; and as the change and impairment of the pupillary reflex is usually the earliest to appear of the characteristic motor symptoms, the extreme importance of this impairment is manifest. It is extremely important to bear in mind that no extravagance of delusion will justify a diagnosis of general paralysis in the absence of motor symptoms, and no impairment of pupillary reflexes will justify a diagnosis of general paralysis in the absence of mental disorder. For the same impairments that are here described occur in *tabes* also.

In addition to the internal ocular paralyses that have been described, motor affections of the external muscles of the eye occasionally occur in general paralysis, but these are rare and quasi-accidental in character, and though they may go to corroborate a diagnosis, they cannot be relied upon for that purpose. Transient ptosis and strabismus have already been mentioned among the prodromata, and may occur in more prolonged or in permanent deviation in a later stage of the disease ; and nystagmus has been observed.

Impairment of the pupillary reflexes is almost always the earliest characteristic motor symptom of general paralysis, but sometimes it is preceded, often it is closely followed, and always it is followed sooner or later, by weakness of the articulatory muscles, which gives to the articulation qualities so peculiar and characteristic that, when they are pronounced, it would be quite practicable to diagnose general paralysis through the telephone, without seeing the patient at all. The impairment of the articulatory muscles, like that of the pupillary muscles, follows a definite order, affecting first the tongue, and thereby the dental con-

sonants and the liquids *l* and *n*; then the lips, and thereby the labial consonants and the liquid *m*; and lastly the larynx, affecting the cadence and introducing a peculiar bleat into the voice.

The defect, like many other motor defects, is not perceptible, in the earlier stage, until the muscles begin to be fatigued. In the first part of a conversation the articulation may be quite free from defect, but presently a word is slurred, then another, and at the end of a long conversation the patient may become almost unintelligible. From the inability to pronounce consonants and liquids, it follows that syllables are run into one another, and words are abbreviated and slurred; the beginning of a word being clearly pronounced, and the end running off into an indistinguishable growl. Often, especially when the disease is in the early stage and the defect is slight, the patient is aware of it, and takes pains to pronounce his words with punctilious and excessive distinctness. In this, as in other respects, the articulation in general paralysis, when not excessively affected, is indistinguishable from that of drunkenness. The words are slurred; their terminations are gabbled; they are run into one another, and syllables and small words are omitted.

The dependence of the articulatory defect upon weakness of the articulatory muscles is shown by the tremor of these muscles when put to uses requiring prolonged and steady contraction rather than rapid movement. When the tongue is protruded, it is tremulous with a tremor that is not fibrillary, but affects the whole organ. When the teeth are bared the lips tremble, and the tremor may extend to the *alae nasi* and the cheeks. Similarly, when the laryngeal muscles are much affected, since their action is more continuous than that of the articulatory muscles, the tremor affects the vocal quality, which assumes a peculiar bleat, which once heard is quite unmistakable. Ordinarily, however, the cadence alone is affected, and then assumes a peculiar monotony, which deprives the voice of expression, and also is very characteristic.

The attacks of aphasia which sometimes, but rarely, occur in the course of the disease are of course on a totally different

footing from defects of articulation. Apart from the loss of speech which accompanies, as a matter of course, the comatose and semi-comatose condition of the crises, and which is merely a part of that condition, true aphasia, with retention of intelligence, is not common in the course of general paralysis.

Conformably with the articulatory defect, which is a loss of the finest, most delicate, most elaborate, and most special of the movements of the muscles of the mouth, occurs subsequently a parallel defect of the muscles of the upper extremity. The movements of the upper extremity which answer the above description are the movements of handicraft, and especially of handwriting, and in general paralysis the handwriting presents very characteristic features. The formation of words is peculiar. Words, syllables, and letters are duplicated, and words, syllables, and letters are omitted, reproducing to some extent the peculiarities of articulation. In addition, the mechanical part of the handwriting is badly done. Letters are badly formed, strokes are shaky and interrupted, and cease to be uniform in strength or thickness. Letters are of unequal size, are left unclosed and unjoined, and the lineation becomes irregular. Some words and letters are above the line, others below, and words, parts of lines, and whole lines, are written obliquely. Blots, smudges, and erasures are frequent. The letter usually begins pretty well, as the conversation does ; but as in the spoken word, so in the written, the latter part of the word is worse executed than the beginning, and as the articulation fails more and more the longer the conversation is continued, so the calligraphy becomes worse and worse the longer the effort of writing endures.

As with each region separately, so with the body in the aggregate, the most specialized parts, performing the most precise and elaborate movements, are the first to fail, while the last to be affected are those which perform massive movements of little accuracy and capable of only approximate adjustment. The tongue fails before the lips, both before the larynx, and this before the muscles of mastication. In the upper extremity, the movements of the thumb and finger fail before those of the

hand as a whole, and these before the movements of the arm. So, generally, the pupils fail before the articulation, the articulation before the handicraft, and the handicraft before locomotion. At length, however, the legs become affected. General paralysis and tabes have the same pathological basis ; they are practically the same disease affecting different portions of the cerebro-spinal axis ; yet, although general paralysis is sometimes engrafted on tabes, a tabetic gait is never seen in general paralysis unless the cord disease has preceded the cerebral disease. The legs become weak, but they do not become ataxic. The patient shuffles and straddles, but he does not dindonate. His gait becomes slow and awkward, he stumbles over stones, and has to be assisted in going upstairs. He cannot turn without stopping and making a manifest effort to do so. As the paralysis increases, he becomes unable to walk, or even to stand ; and at length contracture sets in, and he lies with his arms crossed on his breast, his knees drawn up, and his heels nearly touching his buttocks.

In tabetic cases there are the disorders of sensation that pertain to tabes, but in non-tabetic cases there is no evidence of disorder of sensation, although in the later stages sensations, including those of touch, pressure, and pain, are gradually impaired and at length appear to be wholly, or almost wholly, lost, *pari passu* with the general obliteration of consciousness that takes place towards the end of the disease. In some cases it appears that sensation is impaired earlier than, and out of proportion to, the general dulling of consciousness, for general paralytics will occasionally suffer injuries, and even severe injuries—bruises, cuts, lacerations, and burns—without evincing any very decided complaint or sign of pain.

Early in the disease the patient is usually very 'fit'. His muscular system is as well developed, and his body as devoid of fat, as if he had been training for some athletic contest ; but as he enters the second stage, his activity subsides and his voracity increases, and he lays on fat. As his intelligence decays, his face loses its expression ; the deposit of fat in his face obliterates his wrinkles, and the countenance looks puffy, bloated,

expressionless, and greasy. Then, as the disease still progresses, the accretion of fat is lost, the muscles waste, and the body becomes emaciated. Food fails to be assimilated, the tissues lose their characteristic qualities; sweat and sebaceous secretion are deficient, the skin becomes malodorous and bruises easily; the bones become fragile; the bowels no longer act naturally; bed-sores are hard to prevent, and languid inflammations of various parts are prone to occur. Finally, the patient dies either of exhaustion, or of sepsis, or of the pneumonia of the dying, or in status epilepticus.

Such being the physical symptoms, which are practically uniform in all cases, and present individual variations only, we may now consider the disorders of mind and of conduct, which, unlike the physical symptoms, present wide and surprising differences, and fall naturally into well-characterized groups or types. It is a fact as well established as it is at present inexplicable, that the prevalent type of the disease changes in the course of years. Thirty years ago but one type of general paralysis was known, and the mental and ethnological symptoms of all cases could be included in one description, that of the Classical or Exalted, or Excited, or Maniacal type. About twenty years ago cases were observed in which the hyperbolical exaltation of general paralysis did not exist, but on the contrary the patient was depressed and miserable. The proportion of these cases rapidly increased, until they outnumbered the exalted cases, and then a third type came into view. Cases came under notice with the identifying physical signs of general paralysis, but with neither exaltation nor depression. The patient was merely demented. He exhibited simple deficiency of mind, simple inefficiency of conduct, without any affective disorder. Rare at first, and looked upon as strange anomalies, these cases became more and more numerous in proportion to the others, until, at the present day and in London, they are more frequently met with than either of the other types. The reason of this change of type is very difficult to assign, and of course cannot be assigned with any certainty. One might speculate that it is due to an

altered mode of treating syphilis, years before the general paralysis appears, and other possibilities suggest themselves, but as any such speculations can be only purely fanciful, and cannot at present be verified, it is useless to pursue them. About the fact of the two successive changes in the prevalent type of the disease, there is, however, no doubt, and the mental disorders in the several types are so different that they require separate description.

CHAPTER X

CLINICAL TYPES

THE CLASSICAL OR EXALTED TYPE

THIS is a very strikingly distinctive disease. It may begin by the gradual aggravation of the excited and exalted class of prodromata into subacute or even acute maniacal excitement. The restless activity becomes more and more excessive; the speculations become more reckless; the lust for purchasing more intense; the disregard of convention more complete; the dissipation wilder; until the attention of the family passes into uneasiness, and the uneasiness into alarm, and at length it becomes manifest that the man is out of his mind. In other cases the onset is much more rapid. The vagaries of conduct are manifestly excessive from the first, and in a fortnight, a week, or even less, the condition of acute mania is attained, and the mania is accompanied by an enormous and incredible exaltation. The patient attributes to himself ability, worthiness, and wealth in unspeakable degree. There is nothing he cannot do, no honour great enough for his merits, no enumeration adequate to express his possessions. He can kill people and bring them to life again. He has a hundred bodies. He can be present in a hundred different places at once. He has died and come to life again thousands of times. He has hundreds of wives and thousands of children. He is honoured and revered beyond his utmost capacity to express. He has such titles as never before were given to a human being. He is Lord, Duke, King, Emperor, Saviour, God. He owns houses, banks, towns, countries, universes. His wealth is expressed in millions, trillions, and quadrillions. He invents the most crazy and impossible devices. He will sheathe warships with india-rubber to make the missiles of the enemy rebound from them. He will supply the market with scented needles. He will trans-

port the city of Jerusalem to Shepherd's Bush, and make a fortune by the exhibition. He will make water run uphill by the attraction of a gigantic magnet. He will build a bridge from London to New York or Bombay. He will pay off the National Debt with the proceeds of a book that he is writing. He will abolish poverty by giving every one a thousand a year. Nothing is too grandiose, nothing too grotesque for him to achieve.

With this exaltation of mind he exhibits a curious excess of conduct on a reduced level. He writes orders for enormous purchases of shares, land, furniture, live stock, yachts, and what not, but he pays no attention to the fact that no notice is taken of the orders and that they are never executed. He writes and telegraphs to all the crowned heads in Europe, but he never notices that he has no replies. He arranges with his partner or his manager for gigantic business transactions, but he never inquires whether they are carried out. He distributes cheques for thousands and millions, written, it may be, on margins of newspapers, or on pages torn out of books, and never troubles to ascertain whether there are funds in the bank to meet them. He is up early and late, sleeps little, is full of eager, fussy, futile activity.

He is irascible and impatient of opposition, and is easily provoked to outbursts of violence, but at the same time he is infirm of purpose and easily influenced. His attention is so vagrant that he is easily diverted from his immediate intention and induced to interest himself in something else. In his own house he can be controlled by his own servants, if they are at once authoritative and judicious. Sent to an asylum, he accepts the situation without surprise and without remonstrance. He does not protest against his removal or the control to which he is subjected.

His personal appearance conforms with his mental state. He dresses fantastically, assumes grotesque ornaments, will go out in the street in his dressing-gown and smoking-cap, asserting that the one is a royal robe and the other a kingly crown. He will wear in his button-hole a large nosegay, or a sunflower the size of a cheese-plate.

Such is the character of the outbreak in an exaggerated case of the classical or exalted type of general paralysis ; but not all cases of this type are so pronounced as this. If the attack be milder in character, the subsidence of excitement, which, in any case, occurs after a few weeks from the outbreak, may amount to a complete intermission, and the patient may recover, and return to his work in the world, and transact his duties ably and efficiently for weeks, months, or even years. Usually some indication, in the form of a weakness of will or an impairment of intellect or of moral sense, will remain of the storm he has passed through, but in some cases no trace appears to be left.

In the initial stage of the disease, that is to say, among the late prodromata, in the early part of the outbreak, and often continuing during the intermission, if there be one, is a pronounced sexuality. The patient, perhaps for the first time in his life, consorts with loose women. He keeps a mistress. He is lewd in conversation. He is often open and unashamed in his amours, and gives occasion for notorious scandal. He may forget that he is married or, without forgetting this, he may regard himself as absolved from the ordinary obligations of morality and law, and may become engaged to one or more other women. I have known a general paralytic in the early stage propose to, and be accepted by, a low woman with whom he had not been acquainted more than half an hour.

In rare cases, the recovery, if recovery take place after the initial outbreak, remains permanent, or at least endures indefinitely ; but ordinarily, at the end of a few weeks or months the same symptoms recur, the same exaltation, the same delusions, the same excesses of conduct, are repeated ; and this time the degradation of mind is greater. Now the craving for acquisition, which formerly led him to purchases of inordinate magnitude, exhibits itself in the absorption into his pockets of everything movable within his reach. His pockets are stuffed to excess, and are found to contain a miscellaneous collection of rubbish—newspapers, books, or pages torn from them, bits of bread, meat and pastry, sticks, stones, pencils, pens, chessmen and draughtsmen, cigars, pipes, sealing-wax—anything, in short, that is loose

and portable, and can be stuffed into the receptacle. Now, too, his emotional condition, while less pronounced, is more unstable. He is more easily provoked to rage, more easily moved to laughter and tears; but his rage is less intense and more short lived, and his laughter and tears are similarly transient. In this condition he remains, with some fluctuations, until the first crisis occurs, and thereafter the course of the disease is that already described—a succession of lapses into deeper and deeper incompetence, each followed by a certain degree of recovery, but each recovery less complete than the last.

THE DEPRESSED OR MELANCHOLIC TYPE

Like the classical type, this form of general paralysis usually begins with an outbreak of acute insanity; but, instead of the acute insanity being maniacal in character, it is melancholic or resistive in type. Instead of the excessive and multiplex activity of the character already described, the patient is slow, lethargic, and dull. Instead of rushing, he crawls from place to place, and sometimes he resists every change of whatever kind. He resists having his clothes put on, and having them taken off. He resists being compelled to sit down or stand up. He will not eat if asked, but he will take food furtively from others. He does not often refuse food altogether, nor does he usually exhibit suicidal tendencies, however depressed he may appear; but sometimes he does attempt suicide, usually, however, in a half-hearted manner. His delusions have the usual complexion of delusions of depression, that is to say, they are delusions of incapability, unworthiness, and poverty; but they differ from the ordinary delusions of depression, and resemble those of the exalted type of general paralysis, in their extreme exaggeration—in their hyperbolic impossibility. If he is poor, he is not only ruined, but he is in debt for millions and millions. The whole ocean is liquid faeces. The stench from his body fills the whole world. His bowels have not been moved for years and years. So far from being able to jump over a house, or walk on the sea, he cannot walk across the room, or move a limb.

The melancholic form of general paralysis differs from the classical form in sundry other ways. Its course is more uniform. The crises are less severe, and the intercritical recovery less pronounced. It is sometimes accompanied by hallucinations, which are very rare in the exalted type. The hypochondriacal feature which is usually present is the reverse of the feeling of increased bodily capability which is so characteristic of the form previously described. The duration of the disease is usually longer.

THE DEMENTED TYPE

As already said, this is the type that is now most frequently met with. It begins very gradually. The patient begins to be confused in his mind. He makes mistakes in his work. He is found fault with, and has to take a post of less consequence and less responsibility, and correspondingly his pay is diminished. He forgets things—forgets what he has to do, forgets names, both of persons and of things, forgets his way from place to place. His bodily strength fails, and he suffers from distracting headache. His headache is continuous and severe, and is often the occasion of his seeking advice. When he consults a doctor, the only complaint made may be of headache, and the existence of mental confusion and lapses of memory is not mentioned until it is elicited by questioning. Then the pupils are examined, and the characteristic defects of general paralysis are found. Delusions are wholly absent in the early stage, and are never prominent. If they appear later in the malady they exhibit the exaggerated character that prevails in the other types of the disease. Often there is irritability and ill temper, but it shows itself more as querulousness than as violence, and the outbreaks of violence, so frequent in the exalted type, are rare. The course is more uniform than even in the melancholic type, and the crises usually less pronounced, but sometimes they are severe; and the patient gradually sinks into deep dementia, and finally into the bed-ridden condition, without manifestation of consciousness, in which all types of general paralysis terminate.

THE FULMINATING TYPE

General paralysis varies much in its duration. Commonly, it terminates within two years, or more often three years, of the first definite recognition ; but sometimes, even without intermission, it is spread over ten or fifteen years ; and in a few cases it runs its course with terrible rapidity, and brings life to a close in a few months, or even weeks. Usually the symptoms are of the classical form, and are exaggerated in conformity with the intensity of the disease. The maniacal attack which marks the onset of the classical form becomes, in the fulminating form, an attack of acute delirious mania. In very rare cases the spinal cord is first affected and the legs become paralysed, while the mind is but moderately and occasionally confused, but the confusion soon runs on into utter dementia with occasional outbreaks of excitement, and terminates in coma.

THE SPINAL TYPE

General paralysis always affects the spinal cord sooner or later, and paralysis and contracture of the limbs follow on the affection, but, as this does not usually take place until consciousness is so dulled that conduct would in any case not be expected, the spinal condition does not attract much attention. That the spinal cord affection is an integral part of the disease is shown by the early alteration of the knee-jerks. General paralysis sometimes, however, begins in the cord, and in that case the disease of the cord may exhibit itself as paraplegia, as already described, or as spastic paraplegia, or as tabes dorsalis. It is the last class of cases that are most frequent. Many cases of tabes exhibit infirmity of temper and other mental defects, and in a certain, at present unknown, proportion of tabetics, general paralysis becomes superadded after the former disease has existed for some time. The proportion of general paralytics who have been tabetic has been estimated as high as 25 per cent., but this appears to me a greatly exaggerated estimate, and when it appears that the tabes has been diagnosed merely by absence of knee-jerks and defect of pupillary reflexes, both

of them symptoms of general paralysis itself, it will be seen that the estimate is not entitled to acceptance. Without having statistics at hand, I should guess 5 per cent. as much nearer the mark.

It is said that the cases of tabes in which general paralysis appears are more rapid in their course than cases in which it does not ; but this does not agree with my experience ; neither am I able to concur in an opinion that has been expressed that, when general paralysis appears in the course of tabes, the tabes improves. It is clear that these things occur in some cases, or the assertions would not have been made, but it is certain that they are by no means of universal, nor even of general, occurrence. If I were to say, as the result of my experience would justify me in saying, that the general paralysis that is engrafted in tabes is of very slow course, and sometimes recovers, I should no doubt be guilty of a similarly hasty generalization. The fact is, that the cases in which general paralysis occurs as an addition to tabes are not sufficiently numerous to warrant any general statement with respect to them.

The type of the mental symptoms, when general paralysis occurs in a tabetic, is usually of the classical form. The commencement is by an attack of acute or subacute insanity, and there are delusions of the grandiose and elevated character. Since the pupillary reflexes are already impaired, and the knee-jerks abolished, by the spinal cord disease, these signs are not available as aids to diagnosis, but in their stead the very existence of the tabes itself proves that there is already present in the body of the patient the poison to which general paralysis is due, and when the character of the mental symptoms is taken into account, the nature of the disease cannot be in doubt.

THE CIRCULAR TYPE

The circular type of general paralysis is rare. It begins in the customary way, by an outbreak of subacute, culminating in acute, insanity, with the exaltation, excitement, extravagance, and immorality of the classical form ; and, as in this form, the acuteness of the symptoms subsides in a few weeks. But then,

instead of the relapse that is customary in the other types, the patient improves until he is practically well, and it may be thought that the diagnosis was mistaken, and that the disease after all was not general paralysis. But this course is sometimes, as already described, taken in the classical type of the disease. It is at this point that the variety under consideration takes on its peculiar character. After a few months of sanity, the patient begins to be depressed and gradually sinks into profound melancholia, from which, after weeks or months, he again recovers and returns to active life. Then, after a further interval of sanity, occurs a new outbreak of excitement, and thus the circle is complete. It may be renewed more than once before the characteristic physical signs appear, and the patient lapses into the dementia of the advanced stage of general paralysis.

OTHER TYPES

A hypochondriacal type of general paralysis is sometimes described, but it is not worth while to distinguish this from the depressed type already considered, for the hypochondriasis is nothing but the reflection of the depression in the estimate which the patient forms of his bodily condition ; just as the exaggerated powers and capability of the classical type are the reflections of the exaltations of the sense of well-being that he experiences.

A stuporose type is sometimes described, and this also is so closely akin to the depressed and demented types that it is scarcely worthy of separate description.

More important differences exist when general paralysis attacks women and children, and then it is the more necessary to describe, since the characters are less conspicuous, and the disease more likely, therefore, to be overlooked.

IN WOMEN

The disease is less frequent than in men, in the proportion of one to five or six in the working classes, and in a very much smaller proportion—one to fifteen or twenty—in the well-to-do. The mental symptoms in women are milder than in men ; the

classical type is comparatively rare, the demented type being the rule, though headache is less common in this type in women. The disease sets in usually earlier in life in women than in men—nearer 30 than 40—and pursues a course that is not only milder but more prolonged. The physical, like the mental signs, are usually less pronounced, and take longer to be established, and the crises occur at longer intervals. The whole course of the disease is less acute.

IN CHILDREN

In children and young persons who have not acquired syphilis, general paralysis does not occur unless they are the subjects of hereditary syphilis. Usually the patient has been more or less weak-minded from an early age, but the general paralysis does not occur until the patient is in his or her teens. There is no marked preponderance of cases in either sex, both sexes being equally liable to hereditary syphilis. The course of the disease is similar to that which occurs in women, being of the demented type and of slow progress, with crises at long intervals and of mild character. As in adult general paralysis, there is sometimes a history of a blow on the head, but then it is to be remembered that few persons pass through childhood without an accident of this character. The physical symptoms are the same as in the adult. Seeing that, in adult general paralysis, increased sexuality is frequent in the early stage, it might be expected that juvenile sexual paralysis might be attended by a precocious excess of this function; but this is not the case. On the contrary, the sexual development is usually arrested. It must be remembered, however, that the increased sexuality occurs in adults in the exalted type of the disease, and has not been observed in the demented type, which is that which occurs in children.

COURSE

Whatever the type of the disease, its peculiar features are of importance in the first stage only of the disease; that is to say, from the outbreak of the disease up to the time of the first

fit. After this the special features belonging to the type are still recognizable as long as the patient retains sufficient consciousness and sufficient capability of speech and conduct to manifest them ; but they cease to be important, for now the interest is centred, not upon the manifestations in mind or conduct, but in the struggle of the constitutional powers of the patient to combat the ravages of the disease, and to prolong life in spite of its invasion. In this struggle there is no important difference between the several types, though there are considerable differences between different patients. As a rule, which is not very strictly adhered to, the length of the several stages is proportionate in each case. That is to say, if the first stage is prolonged, so is the second, and so is the third, the first stage terminating with the first definite crisis, and the second with the onset of muscular contraction. And similarly, the shorter the first stage, the shorter usually are the others, and the whole course of the disease. This is the usual course, but it is subject to many exceptions. Progressive as the disease is called, it is always, when closely investigated, seen to be fluctuating in its course, the patient having sudden lapses and gradual recoveries. If, for any reason, the lapse should be long postponed, or should not occur at all, the recovery may be surprisingly complete ; and in the early stage it is not at all infrequent for the patient to recover sufficiently to resume his business and his family relations. Such recoveries are less frequent the more advanced the stage of the disease, but still recoveries to a surprising degree of sanity and efficiency do take place in the second stage, and rarely even after the patient is become bedridden and seems utterly demented. While, therefore, the prognosis is always bad in general paralysis, it should always be guarded and qualified.

The average duration of the disease, from the first definite outbreak accompanied by pupillary signs, is from two and a half to three years ; but it is unsafe to make any definite prediction in an individual case from a knowledge of the average. Nor can the duration be predicted with any certainty from a consideration of the type. Generally speaking, the exalted type is

of longer duration than the demented, and the depressed is longer than either ; but there are many exceptions. Women, in whom the type is usually the demented, usually live longer than men with the exalted type, and of course much depends upon the occurrence, number, and duration of remissions or intermissions. While four years may be regarded as the maximum duration for an ordinary case, there are exceptional cases in which the disease lasts continuously for nine, ten, or twelve years, and there is no certain indication in the early stage to show that this exceptional duration will be reached. I have seen a case of nine years' duration which, as far as symptoms were concerned, was still early in the second stage, and bade fair to live for nine years more. On the other hand, a fulminating case may prove fatal in three or four months, in six or even fewer weeks. Such cases are very rare.

CHAPTER XI

DIAGNOSIS

WHEN general paralysis is fully established, it is one of the most distinct of diseases, and it is scarcely possible to make any mistake in diagnosis. When the articulatory defect is pronounced, it may be diagnosed through a telephone, and when the patient wears a sunflower in his button-hole as in the case already referred to, it might almost be diagnosed through a telescope. But before the disease is fully established, and before the physical signs are distinctive, the difficulty of making a certain diagnosis is often great, and sometimes insuperable.

A very frequent mistake, but an unpardonable one, is to diagnose general paralysis from grandiose delusion alone. Grandiose delusion of very exalted character is frequent enough in paranoia, and in the allied condition of fixed but unsystematized delusion; and, taken by itself, is not in the least significant of general paralysis. Moreover, as we have seen, there are many cases of general paralysis without grandiose delusion, many without any delusion at all. It can scarcely be too often reiterated that general paralysis cannot be safely diagnosed in the absence of the characteristic physical signs; and, when these signs are present, and are accompanied by any form whatever of mental disorder, the diagnosis of general paralysis is justified.

Difficulty arises in those cases, and in those cases only, in which mental disorder coexists with doubtful physical signs; and in the early stage the physical signs are often doubtful. The pupillary light-reflex, for instance, may not be abolished, but it may be sluggish, and yet the observer may well be in doubt whether the sluggish reaction is slow enough to have a pathological significance. Or there may be slight mental confusion lasting for two or three weeks, with occasional lapses of

memory and occasional eccentric acts, and yet the pupils may act perfectly, but one knee-jerk may be distinctly exaggerated. Would it be justifiable to diagnose general paralysis in such a case? Certainly not. It is highly suspicious. It is likely to turn out to be general paralysis, but it is certainly not safe to give a confident diagnosis.

There are many signs which may justify a suspicion, nay even a likelihood, of early general paralysis, but the rule may be laid down categorically that a confident diagnosis is not justified unless the pupillary reflex is seriously impaired. On the other hand, this reflex may be impaired or lost in the absence of general paralysis. The iris may be adherent to the lens. There may be unsuspected cataract in one eye, and I have known this to be a source of difficulty. There may be syphilitic disease of the brain, producing the iridoplegia and mental weakness, but not producing general paralysis, or a patient may have had syphilis, and may consequently suffer from loss of the light-reflex, and yet not be exempt from insanity, which is not general paralysis. If the pupils are small, it may be difficult to be sure whether the light-reflex is or is not present.

In these cases of difficulty there are two other signs that are extremely helpful. These are the presence or absence of lymphocytes in the cerebro-spinal fluid, and the Wassermann reaction. Like the iridoplegia, these are present in syphilitic disease. They are present in general paralysis, in tabes, and in syphilitic meningitis, but as with iridoplegia, the sign is not always conclusive. If the fluid is uncentrifugalized and there are but half a dozen lymphocytes in the field of the microscope, there is almost certainly syphilitic disease. Similarly, if the Wassermann reaction is positive, the malady is certainly parasyphilitic, but if the reaction is negative, parasyphilis is not conclusively excluded.

Such being the chief signs upon which a diagnosis may be made, the following are the diseases with which general paralysis is most likely to be confused:—

1. *Alcoholic Insanity.* The resemblance between alcoholic insanity and general paralysis is often very close, and in some cases the diagnosis cannot be made with certainty until time

makes the matter clear. Like the general paralytic, the subject of alcoholic paralysis suffers from delusions that are often grandiose. He has often a defect of articulation very like that of general paralysis. He is tremulous. His handwriting is often impaired. He is liable to convulsive seizures. His knee-jerks present similar alterations. His conduct is often similar, in that he is over-busy, he writes and telegraphs unnecessarily and to excess, and he makes purchases beyond his means.

Such being the resemblances, the following are the differences to be sought for. The delusions of the alcoholic are never upon the same scale of enormous and hyperbolic exaggeration as is seen in some cases of general paralysis ; but then this extreme exaggeration is absent in a considerable proportion of cases of the latter disease.

The defect of articulation may be indistinguishable, but I have never heard in the alcoholic the bleat which is so characteristic in some cases of general paralysis, but which does not occur in all. The articulation of the alcoholic is less deliberate and the defect less pronounced than in the general paralytic, but a difference of degree cannot serve as a guide in all cases.

Tremor is present in both diseases, and in both is exaggerated, and perhaps exists only, on voluntary movement. The tremor in general paralysis affects chiefly the mouth and cheeks ; in alcoholic paralysis it is often in the forehead, and affects the hands quite early in the disease, which is not the case with general paralysis.

The knee-jerks are altered in the same way in both diseases, but in general paralysis there is more often a difference between the two. In either disease they may be exaggerated, diminished, or absent.

The handwriting is very much alike, but the general paralytic is much more prone to leave out and reduplicate words and syllables.

In both diseases convulsions occur, and the convulsions are alike ; but the convulsions of the alcoholic are provoked by the deprivation of drink, while those of the general paralytic occur without provocation.

The pupils are often unequal in alcoholic insanity, but the light-reflex is not lost. It is, however, not always easy to determine whether the reflex is impaired, and hence this symptom may not clear up our doubts.

The peculiar mnemonic defect of alcoholic paralysis—the obliteration of the memory of recent events, with retention of the memory of those long past—does not occur in general paralysis, and the mnemonic delusion—the clear memory and fixation in time of an event which has never occurred—is rare in this disease, frequent in alcoholic insanity.

Peripheral neuritis, if present, is significant of alcoholism. It does not occur in general paralysis. It is not frequent, however, in alcoholic insanity.

Excess of lymphocytosis of the cerebro-spinal fluid is characteristic of general paralysis.

The history may or may not elucidate the case. General paralytics often drink a good deal, sometimes drink to excess; but it is rare in general paralysis to find the history of long-continued and excessive drinking that is necessary to produce alcoholic insanity. At the same time, such drinking may have been indulged in, and yet we may be unable to obtain evidence of it.

When all these matters are considered, it will usually be possible to come to a definite conclusion as to the nature of the disease, but there will still be cases in which a confident diagnosis cannot be made until the lapse of time increases the definiteness of the symptoms and so clears up the uncertainty.

2. The disease which next most closely resembles general paralysis is gross brain disease. A tumour occupying the anterior lobe of the brain may produce symptoms quite indistinguishable from general paralysis, but optic neuritis does not occur in this disease, and, though headaches may be persistent and severe, frequent vomiting is extremely unusual.

3. From ordinary insanity general paralysis is distinguished by its physical signs, when these are present; but in the early stages there may be a doubt.

4. Syphilitic disease of the brain or its meninges may simulate

general paralysis very closely, the more so since the pupillary reflex is affected and there is lymphocytosis of the cerebro-spinal fluid. The occurrence of optic neuritis, of purposeless vomiting, and of local paralysis, especially of the extrinsic muscles of the eye, favour the hypothesis of that disease.

Treatment. Seeing that general paralysis is dependent on syphilis, it is natural to treat the former disease with antisyphilitic remedies, but no benefit is ever obtained from such treatment. Dr. Forbes Robertson claims to have achieved remarkable results from the use of a serum prepared through the medium of a goat from his bacillus paralyticans, but this mode of treatment is not yet generally available. General paralytics have improved after the administration of urotropine, and they have improved without the administration of this remedy. At present the treatment is symptomatic only, but in this treatment certain facts should be borne in mind. General paralytics are peculiarly susceptible to the action of alcohol, tobacco, and drugs, and should be treated accordingly. Tobacco may be allowed very sparingly. Alcohol should not be given at all, and the administration of drugs should be cautious. The importance of intestinal disinfection has already been referred to.

Prognosis. The prognosis of general paralysis is, of course, bad. The vast majority of cases die within a few years. But it must not be forgotten that the disease is often stationary for long periods; that remissions and complete intermissions do take place; that even as late as the end of the second stage a surprising degree of recovery is sometimes attained; and that, in some cases, the intermission is so prolonged that it must be regarded as a real recovery.

CHAPTER XII

MEDICO-LEGAL ASPECTS

GENERAL Paralysis is fertile in medico-legal problems. The Criminal Courts, the King's Bench Division, the Equity Courts, the Probate Court, and the Divorce Court, are all concerned from time to time in determining the mental competence of general paralytics ; and the transfer of a prisoner, some years ago, from a gaol to a lunatic asylum, where he was found to be in the second stage of general paralysis, and to have on his back the marks of a flogging inflicted for a breach of prison discipline, shows that the disease may escape the recognition even of medical observers, and the unfortunate madman suffer the indirect, as well as the direct, consequences of his malady.

General paralysis commonly begins with an outbreak of acute mania, which may be sudden or very rapid in its onset, or may be the culmination of a gradually increasing mental excitement. When the outbreak is sudden and severe, its nature is rarely in doubt. But when the onset is gradual, the condition may not be recognized as a morbid one, and the instability of the patient's mind may result in outbreaks, on very slight provocation, of violence which may result in his appearance before a magistrate, or even in a criminal court. An altercation in the street, or at a railway station ; a mistake about seats in a theatre ; the disobedience of a child ; or any other trivial annoyance may provoke a general paralytic to serious, and even to frantic violence ; and if the existence of the disease has not been recognized, may lead to consequences both serious and undeserved.

Especially in the exalted type of the disease, the patient's notions of *meum* and *tuum* are very much confused. A man who believes that the whole town is his own private property

may very well consider himself entitled to appropriate anything he sees in a shop, or in a private house, that catches his fancy ; and apart from the existence of any such delusion, or of any delusion, his mind may be so confused that he no longer appreciates the difference between other people's property and his own. That propensity to accumulate small articles in his pockets, that we have seen to be characteristic of the second stage of the malady, may appear early, and he may, in obedience to it, pocket things that do not belong to him, in sheer confusion of mind, and without any *animus furandi*.

Very serious consequences may ensue from the purchasing propensity which is such a conspicuous feature in the early stage of the exalted type. The patient often purchases goods far beyond his means, and enters into contracts that he has no means of fulfilling. These transactions take place in the early stage of the malady, and before it is recognized ; and many families are impoverished by such improvident acts. The great importance of early recognition of the disease is therefore manifest.

Difficult questions often arise under partnership deeds, when general paralytics begin to evince the symptoms of their disease by incautious speculations, and act *ultra vires* of the partnership stipulations.

The increased sexuality, that is often such a prominent feature in the early stage of general paralysis, may raise questions for the decision of the divorce court. Especially in the intermission that sometimes occurs in this stage, the patient may completely regain his intellectual competence, and the only sign of his malady may be exhibited in an immorality that is foreign to his previous nature. The immorality may be accompanied by such a blunting of the moral sense, that the man sees nothing incongruous in bringing his mistress home and introducing her to his wife, or in proposing a common home for the three.

Lastly, the validity of a will made by a general paralytic may be in dispute. It is, of course, well established that a lunatic may make a will, which will be upheld by the Court. The question in every case is whether the testator was, at the time the will

was made, of disposing mind ; and the mere fact that he was then the subject of general paralysis will no more invalidate the will, than the fact that he was suffering from any other form of insanity. There are general paralytics in whom the prominence of delusions, and the confusion of mind, are so continuous, that at no time in the course of the disease are they of disposing mind ; but such cases are by no means the rule. Apart from the relatively prolonged periods of remittance and intermittence, during which the testator may be without question competent to make a will, the disease is, as has been described, a fluctuating one ; and there may be, in the course even of the second stage, days on which he is quite capable of appreciating the amount and nature of his property, the claims of those whom he may or may not benefit by his will, and the nature of the business that he is transacting.

From what has been said will appear the extreme importance of an early recognition of the disease when it exists. By such early recognition we may prevent the unfortunate patient from becoming the subject of criminal charges ; from ruining himself and his family by reckless speculation or improvident purchases ; from becoming involved in expensive litigation ; from having to answer for his conduct in the divorce court ; and we may prevent his family from being impoverished by an inofficious will, or by litigation about a will whose validity is doubtful until determined by the Court.

Chas. Mercier

YAWS

BY

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CHAPTER XIII

PATHOLOGY

Definition. A tropical specific infectious disease, caused by a treponema, characterized by a peculiar granulomatous eruption, and presenting a course somewhat similar to that of syphilis.

Synonyms. In the British colonies the disease is usually called yaws; in the French colonies, *pian*. In Venezuela and other South American countries the name *bubas* is much used. Other local names are *gattoo* (West Coast of Africa), *dubi* (Gold Coast), *framosi* (Calabar), *aboukine* (Gaboon), *tetia* (Congo Coast), *momba* (Angola), *parangi* (Ceylon), *buena* (Burma), *puru* (Borneo, Federated Malay States), *pateck* (Dutch Indies), *tonga* (New Caledonia and Loyalty Islands), *coco* (Fiji), *tona* (Tonga Island), *lupani tono* (Samoa). The term *framboesia* was first used by Sauvage in 1759, on account of the raspberry-like appearance of the eruptive elements. Charlouis, in 1882, suggested the term *polypapilloma tropicum*.

Geographical distribution. Yaws is essentially a tropical disease, as few, if any, genuine cases have been reported from places outside the tropical zone. There are authors, however, who believe that yaws was in the past more widely distributed, and indeed the peculiar disease known as *sibbens* or *sivvens*, an outbreak of which occurred in Cromwell's armies in Scotland during the seventeenth century, and the so-called 'button-scurvy' which prevailed in Ireland about a century ago, are considered by some to have been nothing more or less than yaws. At the present time a skin disease not unlike yaws has been reported by several writers in Greece.

Africa. The disease is very rare in the northern regions of the continent; it is said to be occasionally met with in Algeria; it is apparently unknown in Egypt, though, according to some writers, fairly common in some districts of the Soudan. It is very common on the West Coast, especially on the Gaboon

River, in the Congo Free State, and in Angola. It is also found in Mozambique, in Madagascar, and the Comoro Islands. In Uganda and the region of the Great Lakes it is occasionally met with. Griffith has observed it among the Kaffirs in South Africa, near Kimberley.

Asia. The disease is very common in the Malay Peninsula, Assam, Upper Burma, Siam, Java, Batavia, and is extremely frequent in Ceylon, where the number of cases treated in the Government Hospitals during the last eight years was as follows: 3,646 in 1900, 3,117 in 1901, 3,434 in 1902, 3,254 in 1903, 3,591 in 1904, 3,535 in 1905, 3,606 in 1906, and 3,513 in 1907. The patients treated in hospitals represent only a small portion of all the cases. In India it is very rare, though small outbreaks of the disease have been described by various observers. It occurs in certain parts of China, but is unknown in Japan and the central and western regions of the Asiatic continent.

America. It is very common in the West Indies, and occurs in British Guiana, Venezuela, and Brazil. Cases have been reported from the southern United States, but never from the northern states or from Canada.

Australasia. Although absent from Australia, Tasmania, and New Zealand, it occurs frequently in many of the Pacific Ocean islands, Samoa, New Hebrides, New Caledonia.

History. It has been suggested by Hume, Adams, and others, that framboesia was the disease which afflicted the Israelites during their emigration from Egypt, and that therefore the term *saraat*, in the 13th chapter of Leviticus, does not mean leprosy, as usually translated. Ali Abbas and Avicenna, who wrote at the end of the tenth century, mention a disease called *safat* or *sahafati* with symptoms not unlike those of framboesia, but most authors are of the opinion that the disease referred to by the two Arabian physicians was syphilis. The study of the disease first began to engage the attention of European physicians after the discovery of America. Oviedo y Valdez (1478-1557) describes it in his work 'Historia general y natural de las Indias'. Piso (1648) refers to the malady in his work 'De Medicina Brasiliensi'. Rochefort (1656), Raymond Breton (1665), and Labat (1694) report it from the West Indies, stating that it

occurs frequently among the natives (Caribs), who called it *pyans* or *yaya*. Bontius, in 1718, reported that framboesia was endemic, not only in the West Indies, but also in Java, Sumatra, and other Dutch colonies of the East, where it was known by the name of *Amboyna pox* or *pimple*.

In the days of the slave-trade outbreaks of framboesia frequently occurred in the crowded ships carrying African slaves to America; special hospitals for the isolation and treatment of slaves suffering from the disease were built on all the important estates in the West Indies. Occasionally in the countries in which it is endemic the disease may increase to such an extent as to cause veritable epidemics: an example of such an epidemic occurred in Dominica in 1871, when two special segregation hospitals had to be built for yaws patients.

In 1694 an outbreak of a peculiar disease occurred in Scotland called sibbens or sivvens (*sivvi*, Celtic for raspberry), imported apparently by Cromwell's soldiers; it was not improbably syphilis, but some authors suppose it to have been yaws. The so-called 'button-scurvy' of Ireland, endemic there in the eighteenth century and the beginning of the nineteenth century; the 'radesyge' which broke out in Sweden and Norway in 1710; and the 'mal de Chicot' in Canada, have likewise been considered by some writers to be forms of yaws. Several authors—Breda amongst the moderns—have endeavoured to distinguish between yaws, pian, boubas, and parangi; but those who have had the opportunity of studying the disease in different countries have all come to the conclusion that yaws, pian, boubas, and parangi are simply different names for the same disease.

My own experimental researches in cases of framboesia contracted in different parts of the world (tropical America, East and West Africa, &c.) show that yaws, pian, boubas, and parangi are merely synonyms. Since the time of Labat several authors have upheld the syphilitic nature of framboesia; this theory has been supported until lately by Sir Jonathan Hutchinson. In recent times the disease has been investigated, both clinically and experimentally, by a large number of observers. In 1882 Charlouis proved by actual experiment that syphilis and framboesia are two different diseases. The clinical investigation of

the disease by Numa Rat was also of great value ; his report published in 1891 has become classical.

Among the more recent observers who have investigated the disease in various parts of the tropics are Neisser, Manson, Daniels, Jeanselme, Wellman, Powell, Branch, Martin, Halberstädter, Von Prowazek, Ashburn and Craig, and many others.

Etiology. Different kinds of bacteria have been described as causative agents of framboesia. Ejkmán found some peculiar bacilli ; Pariez observed numerous micrococci ; Powell, in 1896, cultivated a yeast from two cases. Breda isolated from several cases a bacillus which he named the 'framboesia bacillus'. Nicholls and Watts, in 1899, isolated a coccus which, inoculated into animals, failed to reproduce the disease.

In February, 1905, I observed in a case of yaws an extremely delicate, almost invisible, spirochaete or spirillum, as I thought at the time. Schaudinn's discovery of a spirochaete in syphilis, published soon after, induced me to work at the subject in a systematic manner. A preliminary note on the presence of spirochaetes in framboesia was published by me on June 17, 1905, in the Journal of the Ceylon Branch of the British Medical Association ; another communication was made by me at the meeting of the British Medical Association, Leicester, July, 1905 ; and further researches were published in various papers.

Recent publications by numerous authors—Wellman, Powell, Neisser, Borne, Prowazek, Halberstädter, Ashburn and Craig, &c.—have confirmed the presence of a specific treponema in yaws.

Treponema pertenue (Castellani), June, 1905. *Treponema pertenue* (Plate XXV) is an extremely delicate spiral-shaped organism varying in length from a few microns to 18 and 20 microns and even more. It is extremely slender ; some individuals are, however, thicker than others. It does not stain easily, but good results may be obtained with Giemsa's method and also with Leishman's stain, provided the alcoholic solution is allowed to act for five minutes and the subsequent admixture with distilled water for from one half-hour to several hours. Using either of these methods, the treponemata stain purplish ; occasionally a few more deeply stained granules may be seen in the body of the organism. The extremities of the parasite are often pointed,

but, probably owing to the manipulation of the films, forms may be met with presenting blunt extremities, or one extremity pointed and the other blunt. In some individuals one of the extremities may present a large pear-shaped expansion, or a loop-like formation. The number of coils varies from six to twenty or more, but they are as a rule numerous, uniform, and of small dimensions. Occasionally a portion of the treponema shows numerous close uniform coils, while the rest of its body shows no coils at all. Sometimes two treponemata may be attached end to end, or apparently twisted together. So far I have not been able to detect any undulating membrane, though its presence has been asserted by other observers (Blanchard). Occasionally, in preparations stained by Löffler's method of flagella staining, it has seemed to me that some of the organisms present an extremely delicate flagellum at one end. According to my observations, therefore, the organism is in all probability a treponema, but further investigation is necessary to settle its true systematic position. From the above description it is evident that the yaws organism is morphologically similar to that of syphilis, and indeed at first I believed that the two parasites differed biologically rather than morphologically. Blanchard, Mesnil, Prowazck, and others seem to have been able to make out some slight morphological differences between the two. Martin states that the yaws treponema is even more slender and more difficult to stain than the *Treponema pallidum* of Schaudinn. Rivas states that the *Treponema pertenue* is more slender than *Treponema pallidum*, and has closer coils. Prowazck, Levaditi, and Nattan-Larier state that *Treponema pertenue* shows less regularly shaped coils, and one extremity terminates in a loop much more frequently than in *Treponema pallidum*. Personally I believe that the differentiation of the two organisms is to be based more on the result of the biological tests than on slight morphological differences. The animal tests clearly show that the two organisms are two different species, inasmuch as monkeys immunized against *Treponema pertenue* do not become immune for *Treponema pallidum*—the spirochaete of syphilis.

Incidence of the Treponema pertenue in Yaws lesions. The

presence of the treponema is constant in the primary lesion and in the unbroken papules of the general eruption. It may be found in the spleen, lymphatic glands, and bone marrow. In the blood I have not succeeded in demonstrating it microscopically, though there is no doubt that the blood of the general circulation is infectious, inasmuch as monkeys inoculated with it develop typical yaws lesions in which the treponema is abundantly present. The treponema is absent in the cerebro-spinal fluid.

Bacteriological flora found in open sores of Yaws. While *Treponema pertenue* is the only germ found in the non-ulcerated lesions, the ulcerated lesions of yaws are soon invaded by all kinds of germs. Apart from innumerable bacteria, various kinds of spirochaetes are present; one form is rather thick and takes up the stain easily; it is morphologically identical with the *Spirochaete refringens* of Schaudinn. Another form is thin, delicate, with coils varying in size and number, and with blunt extremities; I called it *Spirochaete obtusa*. A third form is likewise thin and delicate, but tapers at both ends; I named it *Spirochaete acuminata*.

Inoculation experiments of Yaws in man. Paulet, in 1848, inoculated fourteen negroes with the secretion taken from yaws granulomata. All of them developed yaws, the inoculation period varying from twelve to twenty days, when at the seat of inoculation in ten cases the first nodule appeared, soon followed by a typical general eruption. In two cases apparently the eruption did not start from the seat of inoculation. Charlouis, in 1881, inoculated thirty-two Chinese prisoners—who had never suffered from the disease—with crusts and scrapings from a case of yaws. The disease developed in twenty-eight of them, beginning invariably at the seat of inoculation. Moreover, he inoculated a native suffering from typical yaws, with syphilis. The inoculation was quite successful, a primary syphilitic sore developing, followed by all the usual types of secondary eruption. That yaws patients are not immune against syphilis is proved also by Powell, who described two cases of syphilis supervening on yaws.

Inoculation experiments in monkeys. Neisser, Prowazek, Halberstädter in Java, and shortly after myself in Ceylon, have

shown that monkeys are susceptible to yaws. I have experimented with numerous monkeys belonging to the genera *Macacus* and *Semnopithecus*, and I have found that positive results are fairly numerous in both genera provided the scarifications on which the framboetic material is deposited are sufficiently deep. Of eight monkeys of the genus *Macacus* and eleven of the genus *Semnopithecus* inoculated by me with scrapings taken from the eruptive elements of yaws patients, five of the first genus and nine of the second gave a positive result. The incubation period varied from a minimum of sixteen days to a maximum of ninety-two. The appearance of the lesions developing at the seat of inoculation was practically the same in all cases, viz. an infiltrated spot, slowly increasing in size and soon becoming moist, the secretion drying into a thick crust. Removal of the crust exposed a raw granulating red surface (Plate XXVI). With the exception of three cases, the eruption remained localised at the point of inoculation, and no other eruptive elements developed. Although in the monkeys of a low class, such as I used, the eruption is as a rule localised to the seat of inoculation, the infection is general, as proved by the presence of *Treponema pertenue* in the spleen and lymphatic glands, besides the local lesions. Halberstädter has obtained a general eruption in orang-utangs. According to my experiments, splenic blood obtained by puncturing the spleen of a patient affected with framboesia can reproduce the disease in monkeys; the inoculation of blood from the general circulation also may occasionally reproduce the disease: the inoculation of cerebro-spinal fluid into normal monkeys has always proved negative. Neisser, Halberstädter, and Prowazek in Java, and myself in Ceylon, have also proved that monkeys successfully inoculated with yaws do not thereby become immune to syphilis, and, vice versa, monkeys successfully inoculated with syphilis do not thereby become immune to yaws. According to Levaditi, monkeys immunized for yaws do not acquire any immunity for syphilis, but monkeys immunized for syphilis may acquire a partial immunity for yaws. According to Ashburn and Craig, monkeys of the species *Cynomolgus Philippinensis* are susceptible to yaws, but not to syphilis.

Is the Treponema pertenue the specific cause of Yaws? The

following facts are in favour of the *Treponema pertenue* being the specific cause of yaws :—

1. In the non-ulcerated papules, in the spleen, in the lymphatic glands of yaws patients, as well as inoculated monkeys, the *Treponema pertenue* is the only organism present. No other germ can be demonstrated either microscopically or by cultural methods.

2. The extract of yaws material containing the *Treponema pertenue* but—so far as our present methods of investigation permit us to say—no other germs, is infective to monkeys.

3. The extract of yaws material from which the *Treponema pertenue* has been removed by filtration becomes inert, and monkeys inoculated with it do not contract the disease.

Predisposing causes. As is the case in other infectious diseases, dirt and other insanitary conditions favour, to a certain extent, the development and dissemination of yaws ; the disease is extremely rare among Europeans, as also among the better class natives who live in good sanitary surroundings, while it is very common among the villagers and low-caste natives who live in uncleanly and overcrowded huts. Sex does not exercise any influence, nor does age to a great extent, though the disease is somewhat more frequently met with in children and young people. The native practitioners of Ceylon are inclined to ascribe an important predisposing influence to certain foods ; some incriminate a sort of fish called *balla mal*, others a fruit known as *rattadel* (bread-fruit), and a kind of grain known as *kurrakan* (nutcherry).

Histo-pathology. The histo-pathology of yaws has been investigated by Unna, Jeanselme, Plehne, Macleod, and more recently by Schüffner, Shennan, Siebert, Ashburn and Craig. I have myself examined the various lesions : my results tally most with those of Macleod and Shennan. In the framboetic papules the surface epithelium is greatly increased in thickness and numerous elongated downgrowths are seen. The epithelial layers show many patches in which the epithelial cells are swollen, vacuolated, and degenerating ; small sharply circumscribed areas are also seen containing polymorphonuclear leucocytes. The layers near the corium and its processes are, however, almost normal in appear-

ance. The connective-tissue corium forms a thin layer from which narrow elongated pupillary processes pass into the epithelium, some of them nearly reaching the surface. The corium is the seat of marked oedema. There is a diffuse cellular infiltration made up of polymorphonuclear leucocytes, large and small mononuclear, eosinophiles, plasma cells, mast cells, connective-tissue cells, and some extravasated erythrocytes. In the older nodules the plasma cells are present in such enormous numbers as to dominate all else. At no point is there any evidence of the perivascular mononuclear infiltration so characteristic of syphilis, nor any endothelial proliferation in the vessel walls. The framboetic lesion also differs from that of syphilis in affecting the epithelium rather than the cutis, in the more considerable oedema, and in the absence, as a rule, of the giant cells. When the framboetic granulomata have reached a certain stage, a very well-marked hyperkeratosis is noticeable. I would call attention to the appearance of the films, taken in the usual way from the granulomata and stained according to Leishman's method. In such films it is interesting to note the presence of a large number of polychromatic red blood-cells of very different size; some much larger than the normal erythrocytes, some much smaller. They are stained deep or light blue instead of pink, and sometimes have a granular appearance. The leucocytes present in the films frequently contain in their protoplasm, and sometimes in their nuclei, roundish or oval more or less deeply-stained bodies, which I believe to be probably polychromatic micro-erythrocytes engulfed by phagocytes. In such films the treponemata are almost constantly found. The treponemata may be put in evidence also in sections by using the Volpino-Bertarelli, or Levaditi's silver staining, as used by Spronk, Shennan, and Schüffner: the examination of sections so stained shows that the parasite is mostly found in the epithelial layers.

CHAPTER XIV

SYMPTOMS AND COURSE

The course of yaws shows a certain similarity to that of syphilis; therefore, as in the latter, for the sake of convenience we may divide the course of the disease into three periods :—

A primary stage, comprising the development of the primary lesion.

A secondary stage, during which the characteristic framboetic granulomatous eruption appears.

A tertiary stage, in which the late manifestations of the disease develop : deep ulcerations, gummatous-like nodules, &c.

This division into three periods is somewhat arbitrary, as tertiary symptoms may appear during the secondary stage. It has been stated again and again that the whole course of the disease lasts from three to six months in children, and six to twelve in adults ; but according to my experience it has a much longer duration, and unless it becomes extinct after the secondary stage it may extend to many years—indeed I believe that in a certain number of cases, although there are periods during which the patient is apparently free from symptoms, the infection is merely latent, and sooner or later gives rise to renewed manifestations.

The Primary Lesion. After a period of incubation varying in time between two to four weeks, characterized often by signs of malaise, rheumatoid pains, headache, irregular rise of temperature, a primary sore appears at the seat of inoculation, which is generally extra-genital. The primary sore is a papule, which after about a week becomes moist, developing a yellowish secretion which dries into a crust (Plate XXVII) ; often at the place of inoculation several papules appear, become moist, and coalesce into a single element covered by a thick crust. If after some days the crust is removed, the primary sore will appear as an ulcer—not rarely of rather large dimensions, with clean-cut edges and a granulating base. This ulcer may heal, leaving a whitish scar, which later

may become pigmented ; or in other cases it may develop into a granulomatous mass, not dissimilar to the granulomata of the secondary eruption, which appear later on, but frequently much larger. This large single projecting nodule is called 'mother yaw' or 'maman pian', in French *patois*. Occasionally round it, before the general eruption begins, several smaller granulomata develop like satellites (Plate XXX). The primary sore never feels indurated ; though it is often painful during the first stage of development, it may be quite painless later ; occasionally there may be pruritus. The proximal lymphatic glands may become hard and enlarged, but they do not suppurate.

The seat of the primary sore is usually extra-genital. The lesion may develop on an old ulceration, an itch pustule, an insect bite, a wound, a vaccination mark ; the smallest abrasion is sufficient for the entrance of the virus. Most of my female patients presented the primary sore on one of the mammae (Plate XXVIII), developing on some crack or abrasion of the nipple and areola. In several other women the primary sore was found on the skin of the trunk, just above the hip, this being due to the custom among the Ceylon women of carrying their child astride of the hip (Plate XXIX) ; any framboetic element present on the scrotum or nates of the child being continually rubbed against the skin of the mother is likely to cause infection in the latter through any slight abrasion already present, or brought about by the friction. In men and children the primary lesion is frequently found on the hands, arms, and legs, but it may develop on any part of the body.

The primary sore may heal before the general eruption begins, but as a rule it is still present when the secondary eruption appears. I had a case in which the primary sore was still present six months after its first appearance, and when the secondary eruption had nearly undergone complete involution. The duration of the primary sore, therefore, may vary between a few weeks and several months. The primary sore leaves a whitish scar, which later on may become pigmented ; in some cases the scar is small and smooth, in others it is large and very thick. It is to be noted, however, that in Ceylon the disfiguring scar so frequently seen is partly due to the custom the natives have of cauterizing the sore, deeply and by very primitive

methods ; in other cases the large disfiguring cicatrix is due to the primary sore having developed on an old ulcer, which on healing leaves a coarse scar.

The Secondary Stage. The general eruption usually begins between one and three months after the first appearance of the primary sore. It is preceded by malaise, headache, severe pains in the muscles, joints, and bones. In some cases there may be fever of an intermittent or remittent type ; the patient, however, is ordinarily able to attend to his work.

The general eruption develops in my experience as follows : Minute roundish papules the size of pin-heads appear on various parts of the body (Plates XXX and XXXI) ; some papules soon show a yellow point or minute yellow crust at their apex (Plate XXXII). Most of the papules remain of practically the same size for many weeks and disappear, leaving occasionally some furfuraceous patches ; others become larger (Plates XXXIII and XXXIV), several often coalescing, and frequently acquiring a dark areola, in natives ; a reddish one in Europeans. Some of the larger papules increase in size and develop into large granulomatous-looking nodules, covered with a crust, honey-yellow or brownish, formed of desiccated secretion (Plate XXXV). If the crust covering the granulomata be removed, there will be seen a raw surface throwing up red or yellowish fungoid granulations, secreting a thin, slightly purulent secretion, which soon dries into a crust again. These framboetic granulomata are of various size, and may be found on practically any part of the body ; they are extremely common on the upper and lower limbs, and on the face ; on the scalp they are very rare ; they may form rings round the mouth and anus, and may enclose sound skin. They may remain of the same size and appearance for months ; often after a few weeks the secretion diminishes and a process of hyperkeratosis sets in ; they then become of much harder consistency, and some of them, especially those on the dorsum of the feet and toes, may be covered with numerous small hard and warty protuberances (Plate XXXVI). In the majority of cases, within three to six months in children, and six to twelve months in adults, the granulomata dry up, shrink, and disappear, leaving dark and deeply pigmented spots, or occasionally non-pigmented

areas, on their site which are most persistent. In some cases the granulomatous eruption may continue for several years, new crops of nodules appearing from time to time in succession. Each framboetic granuloma generally undergoes involution within two to four months, leaving behind a dark area; occasionally, however, the granuloma does not regress so soon. I have among my patients a boy of eleven, who two years ago had a general framboetic eruption; all the granulomata disappeared with the exception of one on the right knee, which is still present (Plate XXXVII). The granulomata are seldom painful unless they develop between the toes, on the soles of the feet, or round the nails. They very often cause itching. The patient often exhales a peculiar offensive odour, which has been variously described as sour or musty; this is probably due to the growth of various bacteria representing secondary infections beneath the crust of the granulomata. I have more especially noticed this offensive odour when the secondary infection is due to bacilli of Vincent's fusiform type, and coarse spirochaetes. In such cases, if the sores are well washed with perchloride solution for two or three days, these organisms disappear, and the smell is no longer noticeable, though the granulomata do not undergo any change. Though the framboetic granuloma is the characteristic eruption of the secondary stage, there are during this stage eruptions of different types, *papular*, *scaly*, and *ulcerative*. An average ordinary case will present at the same time several typical framboetic granulomata, numerous small reddish papules with the epidermis intact, other papules which have become moist and are covered by a tiny yellow crust; several furfuraeous patches here and there, and spots of increased pigmentation at the place of previous granulomata. Occasionally some granulomata break down and large irregular ulcers form, presenting in their centre reddish papillomatous masses, which in my experience do not usually heal spontaneously. At times in the later period of the secondary stage, peculiar roundish or irregularly outlined whitish patches are present, especially on the back and arms, with a surface like a nutmeg-grater; on closer observation these patches are seen to consist of numerous hard, conical papules, containing in their centre an epidermic plug, which is easily

removed, leaving a depression in the papule ; sometimes the plugs are spiny, and in this case the eruption closely resembles *Lichen spinulosus*.

Eruptions on the Palms and Soles. The granulomatous eruption very frequently attacks the soles of the feet ; at first darkish brown or intensely livid spots appear ; the thick epidermis is gradually pierced by framboesial nodules similar to those found in other regions of the body (Plate XXXVIII). This affection of the soles is very painful ; the natives of Ceylon call it ' dumas '. Similar lesions may occur on the hands. The granulomatous infiltration may attack the matrix and margins of the nails (framboetic onychia and paronychia). The nails become thickened, dry, brittle, and may be cast off entirely, though later they grow again.

After the granulomata have disappeared—occasionally at the same time—peeling whitish patches may be seen on the palms of the hands and soles of the feet, closely resembling the syphilitic *Psoriasis palmaris* and *plantaris* (Plate XXXIX).

Peculiar pitted appearance of the Palms (Plate XL). In several cases in the latter part of the secondary stage, I have observed on the palms and wrists hard, round, and flattened papules or small nodules, having a thick, hard, epidermic plug in their centre ; this plug falls off spontaneously or is easily pulled out ; a deep depression remains ; the papules gradually disappear, but the depressions remain and the palms acquire a peculiar pitted appearance. This condition of the palms may remain unchanged for several years after all symptoms of yaws have disappeared. A somewhat similar appearance of the soles of the feet is occasionally met with.

Lesions of the Hair and Nails. I have never noticed any change in the appearance of the hair, nor alopecia. A few hair follicles may be destroyed when the granulomata develop on the scalp ; which, however, seldom happens.

Mucous Lesions. These are not very common : during the secondary stage small granulomatous nodules may develop at the base of the tongue, also whitish patches closely resembling syphilitic leukoplakia ; small granulomata may develop on the nasal mucosa.

Constitutional Symptoms. Fever. As already stated, fever is frequently present, of an intermittent or remittent type, before

the general secondary eruption begins. During the secondary stage it is usually absent unless complications supervene.

Lymphatic Glands. In a number of cases various groups of lymphatic glands are found to be enlarged. The enlarged glands are roundish or spindle-shaped, hard, painless, and never come to suppuration unless a secondary pyogenic infection is present; the cervical and inguinal glands are most frequently enlarged.

Alimentary System. As a rule the digestive functions are not disturbed. In children slight diarrhoea may be occasionally noticed, preceding the general eruption. The spleen and liver are frequently found enlarged in children, but this is probably due to previous or concomitant malarial infection. The microscopical examination of the faeces of yaws patients will frequently reveal ova of various worms—*Ascaris lumbricoides*, *Trichiuris trichiura*, and occasionally *Ankylostoma duodenale*; but these are of frequent occurrence also in normal natives.

Respiratory System. As a rule the respiratory, as well as the circulatory system, is not affected; occasionally small granulomatous ulcers are to be found in the nasal mucosa and, more rarely, in the larynx.

Locomotor System. Joints. In some patients several of the large articulations may become swollen and very painful. The condition is often of an acute character, and may be accompanied by fever, so that an attack of articular rheumatism complicating the framboetic infection might be suspected. Sodium salicylate, however, is not beneficial, while the administration of large doses of potassium iodide speedily reduces the temperature to normal, and causes the swelling of the articulation to subside. At other times one articulation only is involved, and the symptoms may become so serious as to suggest purulent arthritis. In many cases the smaller articulations become involved; the symptoms in such cases are not acute, and there is usually no fever.

Bones. Inflammation of the periosteum of various bones is of common occurrence. Very frequent is a form of multiple periostitis of the digital phalanges, the cause of the 'multiple dactylitis' so often seen in yaws patients.

Muscles. Contractures of various groups of muscles may be observed; fairly common is a contracture of the flexor muscles

of the forearm ; this contracture is often permanent, and in my opinion is probably due to pathological alteration of the peripheral nerves, rather than being of direct muscular origin.

Nervous System. Neuritis. Neuralgic pains are often observed, but also a true form of neuritis must be admitted ; I have seen in several cases clear symptoms of neuritis of the sciatic nerve, with severe pain along the course of the nerve, and signs of motor and trophic disturbances.

Hyperidrosis. In several of my patients I have noticed hyperidrosis. The phenomenon was limited to the face in some cases, to the hands and soles of the feet in others ; it never extended to the whole body, and always affected symmetrical regions. Hyperidrosis is more frequently observed in children than in adults. In one case—a boy of 14—presenting a general eruption of framboesia, the hyperidrosis of the face was so marked that large drops of perspiration were continually dropping down. I treated him with potassium iodide ; after a month the granulomata had disappeared and the hyperidrosis was no longer noticeable. In some cases the hyperidrosis ceases suddenly without treatment ; the condition, however, may last for some weeks or months.

The Eyes. Granulomatous and papular eruptions may develop on the eyelids. A slight periostitis of the orbital margin is not rare, the margin becoming thickened and very painful on pressure. The occurrence of iritis is denied by most authors. I have seen two typical cases occurring during the general granulomatous eruption ; in both cases the affection was of moderate severity : there was photophobia, ciliary congestion, discoloration of the iris ; pupillary reaction was almost absent. Both cases recovered on large doses of potassium iodide, without any local treatment.

The Genito-urinary System. The primary lesion is rarely found on the genital organs ; in fact, in all the cases I have seen, which amount to several hundred, the primary lesion was always extragenital. Eruptions of the secondary stage, papular and granulomatous, frequently involve the skin of the penis and of the labia ; granulomatous ulcerations may be found on the vaginal mucosa.

The urine, as a rule, does not contain anything abnormal ; unless there is fever, as, for instance, when the articulation

are acutely involved, when a slight amount of albumin may be present.

The Blood. In all my cases in which the blood was examined, a certain degree of anaemia, never very severe, was present. The number of red blood corpuscles varied from 3,000,000 to 4,000,000, the haemoglobin index (Fleischl) from 50 to 75. The red blood corpuscles did not show anything abnormal in their shape. On several occasions I noticed a comparatively large number of polychromatic erythrocytes staining blue instead of pink with Leishman's method. Many of these basophile red cells are micro-erythrocytes. The leucocytes varied from 7,000 to 11,000 per c.mm. In the majority of cases an increase was noticeable in the number of the large mononuclears, even when there was no sign and no history of malaria. In almost all the cases the eosinophiles were increased, this being probably due, in part at least, to the presence of intestinal worms, as revealed by the microscopic examination of the stools, which showed frequently ova of *Ascaris lumbricoides*, *Trichiuris trichiura*, and, in a few instances, of *Ankylostoma duodenale*.

Cerebro-spinal Fluid. In three cases of typical yaws I have performed lumbar puncture, collecting in each case about 22 c.c. of fluid. The liquid was in all cases perfectly clear, like distilled water. The pressure was not increased. The physical and chemical characters were alike in all cases, and apparently did not show much variation from what is found in normal conditions. The density varied between 1.003 and 1.005.

A certain amount of globulin was present, and a substance (dextrose ?) reducing Fehling's liquid. This reducing substance was, in two cases, distinctly in excess of what is observed in the normal fluid. No cholin was found. The reaction of the fluid was alkaline. In two cases the centrifugalized liquid examined microscopically did not contain any cellular elements; in the third case a few extremely rare mononuclear cells were found. The liquid was sterile; no treponemata could be detected.

Tertiary Stage. The disease often terminates with the secondary stage; in some cases, however, the infection does not become extinct, and tertiary lesions appear. Sometimes the secondary and tertiary stages merge into each other, but frequently

the tertiary symptoms appear after the lesions of the secondary stage have undergone complete involution. The interval of time varies considerably in length, and may extend to many years. The characteristic lesions of the tertiary period are gummatous-like nodules and deep ulcerative processes (Plate XLI). These gummatous nodules may develop in any tissues. When developing in the skin and subcutaneous tissues they are indolent, and by their softening and breaking down ulcers are produced, which may present clear-cut margins and a granulating base; when several contiguous nodules break down, serpiginous ulcers are left. In other cases, deep irregular-shaped ulcerations with very thick and undermined edges are seen; in others, large fungating ulcers are present (Plate XLII). On healing these various ulcers leave whitish scars, which are often thick and disfiguring; frequently the scar-tissue undergoes retraction, and causes thereby permanent contractures and disfigurement. Lesions of the osseous type are very frequent; painful nodes developing under the periosteum of several bones—ribs, sternum, &c. In other cases a diffuse chronic periostitis is present, altering the normal shape of the bones. Contractures of various groups of muscles are frequently seen. Tertiary affections of the internal organs and of the central nervous system have not yet been described; I believe that future investigation will prove that they do occur in some cases. It is also probable that further research will show that yaws may be hereditary, though it is worth noting that, in contrast to syphilis, parents generally contract the malady from their children.

Communicability. Yaws is usually conveyed by direct contact from person to person; it appears, however, that the germ is unable to enter through the normal skin, but that there must be some pre-existing abraded surface or small wound or ulceration. Women are frequently infected by their children, the primary lesion appearing often on the mammae. In the native women of Ceylon the primary lesion frequently develops on the skin of the trunk just above the hip, slight abrasions caused by friction being usually present on this part owing to the habit they have of carrying their child astride of the hip. In my opinion, however, there can be little doubt that, in certain cases, insects may carry the disease. It is very noticeable that flies

eagerly crowd on the open sores of yaws patients. In the hospitals, as soon as the dressings are removed, the framboetic ulcerations become covered with flies, sucking with avidity the secretion, which they may afterwards deposit in the same way on ordinary ulcers of other people. Ants also are occasionally seen to go on to the framboetic ulcerations as well as on to ordinary ulcers.

In Nuttall's classical work on the rôle of insects as carriers of parasitic diseases, several authors are quoted (Alibert, Hoish, Cadet, Wilson) who believe that the infection may be conveyed from one individual to another by flies. Wilson states that this belief prevails among the natives of the West Indies.

I made some experiments to prove that flies are instrumental in the dissemination of the disease. A number of flies were fed on scrapings from slightly ulcerated framboetic papules. The flies (*Musca domestica* and allied species), before feeding on the framboetic material, were examined; the examination showed that they did not harbour any treponemata either on their mouth-organs or on their legs. On examination after feeding the majority presented coarse spirochaetes, and a few of them also *Treponema pertenuë*. In another experiment, flies fed on yaws material were placed on scarified spots over the eyebrows of several monkeys and kept there for two hours by means of strips of gauze smeared with collodion at their margins; one of the monkeys became infected.

Prevention of Yaws. In countries where yaws is endemic, the slightest abrasions of the skin should be taken care of and treated with antiseptics. Yaws patients should be prevented from mixing with the rest of the population, and should be isolated in special hospitals till the disease is cured. Their skin lesions should be properly dressed and thus prevented from becoming a source of infection through the agency of flies and other insects; their huts and belongings should be thoroughly disinfected.

Diagnosis. In countries where the disease is endemic, the diagnosis is generally easy, the framboesiform nodules capped with yellow thick crusts being typical. By some observers the disease has been confused with *Verruga Peruviana* and with syphilis.

Verruga Peruviana. This disease is strictly limited to certain valleys of the Andes at an elevation of from 3,000 to 10,000

feet. It is far more deadly than yaws, the mortality rising to 30 and 40 per cent. It is usually accompanied by severe fever of long duration, and its eruptive elements, unlike those of yaws, frequently attack the various mucous membranes and bleed with great facility.

Syphilis. By some authors yaws has been looked upon as a form of syphilis. The results of experimental investigations on yaws and syphilis prove conclusively that the two diseases are distinct, inasmuch as :—

1. Patients suffering from syphilis may contract yaws : patients suffering from yaws may contract syphilis.

2. Monkeys successfully inoculated with yaws do not acquire an immunity against syphilis, and vice versa.

Syphilis has a world-wide distribution ; yaws, on the other hand, is restricted to certain parts of the tropics. Yaws is extremely common in Ceylon, extremely rare in India. Syphilis is common to both countries. In Samoa, according to Turner, syphilis was unknown up to at least 1880, while yaws has been endemic there ever since the group was discovered. In Fiji, too, up to a few years ago, syphilis was not present, while yaws was almost universal. Daniels has made the interesting observation that, in British Guiana, yaws of late years has disappeared, while syphilis is still rampant.

As regards clinical features, yaws differs from syphilis by the following characters. The primary lesion is as a rule extra-genital ; the principal type of eruption is a papule which proliferates into a framboesiform granulomatous growth ; there is an extremely well-marked pruritus. The histo-pathology differs also in the two diseases : in yaws the proliferative changes of the epidermis are much more marked, the granulomata present a more diffuse plasma-cell infiltration, and their blood-vessels have no tendency to the thickening of their walls, which is so characteristic in syphilis. Giant cells are generally absent. Naturally, these differential histological details must be considered collectively, as there is no individual histological character which, exceptionally, might not be present in both syphilis and yaws.

Boubas and Pian. Some of the older authors believed that under the names of yaws, boubas, and pian, three different diseases

were indicated. Among the moderns, Breda, till recently, held the same opinion. All the observers, however, who have had an opportunity to investigate yaws in different parts of the tropics, have come to the conclusion that these various names are simply local synonyms indicating the same pathological entity. My comparative experimental investigations have led to the same result, inasmuch as I have been able to demonstrate that monkeys successfully inoculated with Ceylon yaws become immune to boubas and pian, and vice versa.

Prognosis of Yaws. The prognosis is not serious as far as life is concerned. In 1907, in the Ceylon Hospitals, 3,513 cases were treated, with forty-five deaths; in 1905, 3,535 cases, with twenty-five deaths; in 1904, out of 3,591 cases, sixteen died; in 1903, out of 3,254 cases, only ten died. The prognosis is far more serious in children than in adults. When the disease ends fatally, the termination is generally due to secondary infection, the framboetic ulcerated lesions becoming phagedaenic, and giving opportunity to septicaemic and pyogenic processes to develop. Though yaws rarely terminates in death, its long duration and great contagiousness render it a serious malady. The patients suffering from it are unable to attend to their work; epidemics of yaws, therefore, are of the greatest consequence on tea, sugar, and other plantations, as they reduce the supply of labour.

Treatment. The natives treat the disease in various ways. In Samoa the patient is rubbed down with sand and washed in the sea; after which the yaws are scraped with a shell. In the West Indies, boiled and beaten-up leaves of the 'physic nut' are applied, or powdered alum and sulphur used. In Ceylon, the *vederales* (native doctors) apply concoctions of various herbs and give decoctions of sarsaparilla and other roots. They also use mercury, disguised in various ways. The majority of European practitioners use mercury and potassium iodide; others affirm these drugs to be quite useless, and believe that cleanliness and good and abundant food are quite sufficient to bring about a cure.

In the Colombo Clinic for Tropical Diseases I have made some experiments on the various treatments, and I have convinced myself that the potassium iodide treatment is the most

effective of all. I do not deny that some cases may recover spontaneously, but this is certainly the exception, not the rule.

The potassium iodide should be given in large doses (at least 3 to 4 grms. daily); I have little doubt that many reported failures of the treatment are due to the insufficient quantity of iodide administered, though occasionally cases are met with refractory to potassium iodide or to any other treatment. The yaws patients usually bear large doses well; when severe symptoms of iodism set in, the doses should be temporarily decreased, or the treatment may be stopped altogether for a few days. Mercury, according to some authors, may be of use in some cases, especially in children, but it is, as a rule, far less efficient than the iodides; in fact in my experience its action is practically *nil*.

Atoxyl has been tried by Neisser on monkeys experimentally inoculated with the disease, and by me on human patients: the results are fairly good; in some very stubborn cases a course of potassium iodide followed by atoxyl or soamin injections (grm. 0.25 atoxyl every other day) can be advised. An important point, often forgotten by the practitioner, is that the treatment should be prolonged for a considerable time after the complete disappearance of the eruption, inasmuch as clinical experience, as well as experiments on inoculated monkeys, proves that the specific treponemata may, and do, persist in the lymphatic glands and internal organs long after the cutaneous manifestations have disappeared.

Local treatment consists chiefly in keeping the skin scrupulously clean and washing the eruption twice daily with a perchloride of mercury solution (1 to 1,000), which greatly allays the itching. The ulcerated lesions may be dusted with iodoform, euophen, or boracic acid. Mercury ointments may be beneficial, but in my experience are not sufficient to hinder secondary pyogenic infections. Caustics are not called for unless the ulcers become phagedaenic; in such cases pure carbolic acid is best. Though the external treatment may be useful, one must bear in mind that it is not, as a rule, sufficient alone to cure the disease.





Yaws. The *Treponema pertenue*, drawn by camera lucida,
magnified 4,000 diameters.

PLATE XXVI



Experimental inoculation of Yaws in a monkey.



Primary lesion of Yaws below the right knee.

PLATE XXVIII



Yaws. A typical excavated primary lesion in the breast.

PLATE XXIX



Photograph showing how Ceylon women carry their children, the primary lesion being often found in such women above the hip.



Yaws. The primary lesion with several satellites.



General eruption of Yaws in the early secondary stage.



Yaws. Early secondary eruption.



Yaws. Secondary eruption at a later stage.



Yaws. A type of late secondary eruption.



PLATE XXXV.—Yaws, typical granulomatous eruption.

PLATE XXXVI



The same patient as in the preceding plate at a slightly later stage.



Yaws. A persistent Granuloma surviving over two years after inoculation.



Yaws. Granulomatous eruption on the soles of the feet.

PLATE XXXIX



Yaws. Palmar granulomatous eruption.

PLATE XL



Yaws. Peculiar pitted appearance of the palms.



Tertiary ulcerations in Yaws.

PLATE XLII



Yaws. Tertiary lesions.

SOME MEDICO-LEGAL ASSOCIATIONS
OF SYPHILIS

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CHAPTER XV

SOME MEDICO-LEGAL ASSOCIATIONS OF SYPHILIS

THE fact that syphilis is as well a shameful disease as potentially, in its results, a very terrible and permanent affliction assures for its victims a notorious place in the province of clinical jurisprudence. Further, the fact that the morbidity of the illness is more marked than the consequent mortality accentuates rather than minimizes this sinister position.

In a technical treatise it is sufficient to consider the forensic aspects and occasions which appeal to the medical practitioner—his duties, his risks, his liabilities—rather than to consider such matters as either the use and abuse of Contagious Diseases Acts and other such methods of legislative control of this disease, or the actual legal position of patients, already infected with the virus, who may appeal tacitly or vocally for practical advice in solving a dilemma in prospect or in warding off a charge in pursuit. It is the bounden duty of a medical adviser to make certain that an infected patient realizes and fully appreciates the serious import and importance of the clinical facts and fears of his case, and, if necessary, to urge upon him the exercise of the moral and possibly the legal obligations of the situation. In these matters, however, the medical practitioner must never attempt to offer amateur legal advice to the actual or to the potential victim; occasionally the medical adviser can drop a pertinent hint, but his best course is to say something similar to what the 'First Aid to the Injured' student is told—'Go at once to a trustworthy solicitor!' For his own protection against the malicious and against the litigious, every medical practitioner should become permanently associated with a recog-

nized society for Medical Defence, and should thereafter refer all complaints and threats to the office of that society.

Patients may apply for medical advice upon matters other than the specific infection, which may be discovered incidentally during the clinical examination. On the other hand, patients often possess in this connexion definite private knowledge which they will neither divulge nor acknowledge, even when under formal oath in a court of law. Hence the medical practitioner is, in such cases, left to his own resources in discovering the origin and the nature of the complaint: he may find it wise, upon consideration, tacitly to treat the disorder and its victim without revealing his diagnosis; especially may this be the better plan with innocent, nervous, or impressionable patients. It is common experience to find that many sufferers, upon the principle 'Out of sight, out of mind', will neglect and will even decline to continue routine medical treatment when once the obvious signs of the disease are abated; hence the need of seriously warning all patients of the grave possibilities and the advisability of not too emphatically assuring patients that their malady is 'easily curable'. Care should be taken faithfully to warn patients against the advertised wiles of fraudulent quacks.

The medical practitioner may be invited by the patient or by another cognizant of his condition to explain the position of affairs to the actual or prospective members of the patient's family; such a request or consent so to do should be obtained in writing from the patient. Very great tact and consideration will be called for in the execution of this office: it may be necessary to explain, as Laurence Sterne had found from grim personal experience, that 'these taints of the blood laid dormant twenty years' ('Letters,' 1767).

In the coroner's court it is sometimes alleged that the existence of recently acquired specific disease may have been the motive which prompted the victim's suicide, although the fact of such infection may have been quite unknown to the nearest friends of the deceased person. Similarly, it may be necessary to infer a remote infection in order to explain an aneurysm, tabes

dorsalis, general paralysis, ptosis, sterility, or so-called 'habitual' abortion; the stigmata of hereditary syphilis may demand a similar inference with respect to the parents concerned.

Accusations of clinical negligence in diagnosis or in professional advice and treatment or in both, and allegations of a breach of professional secrecy and of defamation of character, by the public mention of the nature of a patient's disease, are the common pitfalls which beset the paths of members of the medical profession in this direction. To obviate the possibility of any one of these charges a wise tongue and a general knowledge of the prevalent present-day views of the malady are essential; for, apart from private clinical considerations, opinions may be asked in court on such details as the infectivity of the successive stages; whether the disease was congenital or acquired; the limitations of 'Colles' Law'; the possibility of receiving or of giving the infection from sources other than impure coitus; the dangers incident to the wet-nursing of infants, as instanced by the case reported from Paris in 1904, where a State-child infected its foster-mother, who was consequently awarded damages; and the dangers associated with 'arm-to-arm' vaccination, as instanced by the experiments of Dr. Robert Cory (ob. 1900) upon himself. Dr. F. Aurientes deals fully with this side of the question and gives many French references in his Paris Thesis (1906).

It must continually be remembered that in law it is regarded as a criminal indecent assault to examine the physical condition of one person at the request of another person, without the former's full and intelligent consent and assent or, in the case of children, of those *in loco parentis*. In the Armstrong abduction case (1885), which led to the passing of the Criminal Law Amendment Act, a medical man of high standing was reprimanded for assisting in a case where a midwife was held by Mr. Justice Lopes to have committed an indecent assault upon a girl under the age of sixteen years by examining her upon her consent alone.

THE DIAGNOSIS

The diagnosis, whether correct or incorrect, will be the basis upon which many subsequent legal complications, if such arise, will be founded. The patient may offer little or no aid in elucidating his plight, he may in fact repudiate a persistent insinuation on the part of his medical adviser of the possibility or actuality of specific infection ; nevertheless, it is the duty of the practitioner to decide whether the patient is suffering from syphilis or not, and forthwith to treat him accordingly. A mistaken diagnosis will lead to mistaken treatment, to wrong drugging and to consequential dire results both to the patient and to his personal acquaintances. Similarly, unfounded hints made by the medical adviser may injure a patient's social reputation : thus, at the Liverpool Summer Assizes, 1905, the alternative diagnosis of scabies or syphilis led to legal proceedings (*Hobson v. Dr. Bicknell*). In examining the bodies of very young girls, who are in some degraded classes kept in a continually filthy state, a diagnosis of syphilis has been declared, supported by the specious evidence of a previous alleged criminal assault committed by a man suffering from venereal disease—often in poor districts, under the impression that by such nefarious proceeding the disease will be cured by being passed on ; in some of these cases the real disease has been *noma vulvae*, solely the result of the absence of personal and local cleanliness.

CLINICAL NEGLIGENCE

‘Negligence,’ in law, ‘is the omission to do something which a reasonable man guided by those considerations which ordinarily regulate the conduct of human affairs would do, or doing something which a prudent and reasonable man would not do.’

Clinical negligence may lead either to a civil action for damages or to a criminal prosecution. Acts of omission as well as acts of commission may be the foundation of a complaint in this connexion : in technical matters it is as much the duty of the skilled

adviser to enunciate what should not and must not be done as to order definite positive directions for a patient to follow.

Clinical Negligence by Omission. In all cases where patients suffering from syphilis are being treated, serious advice and warning must be given as to the dangers run both by the patients and by others with whom they associate. A patient who cannot be treated with safety and with a likelihood of sexual rest should be advised segregation or seclusion, if necessary in a Lock Hospital. Mutual allegations of negligence may result when the above precautions have not been definitely indicated. Examples of the evil consequences which may follow such negligence may be instanced. It is essential to warn nurses of the dangers attending such cases, both for the sake of the health of the nurses and of the other patients; a nurse may otherwise be infected by a patient whose condition was unknown to her and unrevealed by the medical adviser; all such patients should have a separate set of utensils. A foster-mother acting as a wet-nurse and the nursling infant may either be responsible for the other's infection; it may be noted in this connexion that a child afflicted with congenital syphilis may have no obvious lesion until at least a month after its birth. General domestic servants and industrial employees may similarly be the active or passive agents of infection. The late Mr. Simeon Snell reported several cases in the glass-blowing trade which might have led to industrial compensation ('British Medical Journal,' 1908, vol. i, p. 1678). In France it is a criminal act for a wet-nurse to take charge of an infant if she knows herself to be suffering from this disease.

It is, however, in matters matrimonial that the duties of medical practitioners need the greatest care and tact in performance when either of the parties is known to be the victim of syphilis. It is the function of the medical adviser in such cases to bring all the legitimate professional pressure possible to bear upon the infected party in view of preventing at once the communication of the disease to the innocent and the resulting prolonged mental and physical misery of both.

In the case of a man intending shortly to marry, if he is not

in a fit and safe condition physically it must be made clear to him the risks he runs with respect both to his own reputation and to the health of his fiancée and their possible offspring. The need of immediate and continued treatment and of the postponement of the nuptials must be enforced. The long-extended clinical experience of Sir Jonathan Hutchinson may be quoted : ' If a patient is wishful to marry, mercurial treatment should be continued for two years from the date of the chancre. If the treatment has been continued for that time it is safe for the man to marry. But a much longer period is necessary in the case of a woman. A few cases have occurred in which inheritance has been reported although the interval was much longer than two years, during which treatment has been pursued, but they are very exceptional. It is an open question whether, when transmission occurs in the tertiary stage, any modification in the infant ensues, that is to say, whether there can be an inheritance from a patient in the tertiary stage which shall not evoke exactly the ordinary rôle, or whether the patient shall develop other phenomena more nearly allied to the tertiary stage. There is abundant evidence that a parent suffering from tertiary disease may yet have quite healthy children. There is no reason for believing that syphilis can be transmitted to the third generation.' ('Transactions of the Hunterian Society, 1906'; see also Dr. A. Ravogli's 'Syphilis in its Medical, Medico-legal, and Sociological Aspects', New York, 1907).

The practitioner may not hear of the existence of the disease in a patient until after marriage ; he is bound thereupon to be very circumspect in action and to see that as little matrimonial friction and rupture occurs as it is within his province to arrest. A pristine infection may have been forgotten by the man, so that post-nuptial duties may be performed without any suspicion or fear ; infection may be conveyed to the partner which may lead to a charge of recent unfaithfulness or to a visit to a medical man skilled in the diseases peculiar to honeymoon resorts. In any case, it will be imperative to separate husband and wife until all risk of possible infection or re-infection is passed ; probably

the best method is to send one away from home while the other is being treated: a suitable excuse must be available for so doing. Catastrophes such as these may continue their history in proceedings for divorce on the grounds of adultery or cruelty. Mr. Justice Bucknill, at the Nottingham Autumn Assizes, 1907, while explaining that the acquisition of syphilis by the wife was a sufficient ground for divorce, expressed the opinion that it ought to be made a criminal offence for a man wilfully to communicate a venereal disease to his wife. This opinion is certainly reasonable when it is recalled how severely those are dealt with, under Public Health legislation, who wilfully expose themselves in public while they are aware that they are suffering from a notifiable infectious disease. The legal position is fully discussed in Vol. 85 of 'The Law Times' (p. 214), and, more recently, in Vol. 37 of 'The American Law Review' (p. 226).

Clinical Negligence by Commission. More commonly clinical negligence is exhibited in deeds of commission; similarly a medical adviser may be appealed to where patients have been infected by what is almost the criminal negligence of another person. 'Arm-to-arm' vaccination, without a previous thorough examination of the donor's state of health, is a possible example of medical negligence. Patients, again, may be attended by practitioners whose instruments or who themselves are in a state of dangerous infectivity. Thus in 1874, Dr. Davey, an East End London general medical practitioner, was mulcted in £500 damages at the suit of a plumber and his wife, on the ground that the defendant had attended the woman in child-birth while he was suffering from a poisoned right index-finger; this digit had been sore for two months and had been swabbed with carbolic acid; nevertheless it was held to be the means of infecting the patient with syphilis and the damages were awarded. At the Leeds Spring Assizes, 1883, Mr. Justice Day convicted an aged midwife who had conveyed specific disease to forty-eight of her patients.

Reverting to the value of syphilitic infection as a ground for divorce, it appears (a) that an actual communication of the

disease is necessary and not a mere fear of infection. Cases cited on this point are *Collett v. Collett* (1837), *Ciocci v. Ciocci* (1854), *Jones v. Jones* (1860), *Brown v. Brown* (1865), *Morphett v. Morphett* (1869). Lord Stowell, in *Popkin v. Popkin* (1794), said, 'The husband has a right to the person of his wife, but not if her health is endangered,' and suggested that a reasonable apprehension of injury would be a sufficient ground. In the *Ciocci* case Dr. Lushington said: 'Whoever does an act likely to produce injury and injury follows, can never excuse himself by saying that he hoped a probable consequence might, by some good fortune, not follow.' (b) The innocent party who suffers from infection must of course have been ignorant of the nature and presence of the disease while it was being communicated. (c) The disease must have been passed on knowingly and wilfully; this does not mean that there must have been a desire to communicate the disorder (*Boardman v. Boardman*, 1866); probably also the absence of a local lesion and the belief of the guilty party that he was cured would be important points to urge in defence (*Jones v. Jones*, 1860).

In *Berry v. Berry* (1875) it was held that wilfully communicated venereal disease is evidence of adultery and matrimonial cruelty by the husband and so can substantiate a claim for judicial separation. The existence of venereal disease in a husband is some evidence of an act of adultery on his part—it is merely a question of the strength of the explanatory circumstances. In this connexion it must be remembered that a condition of a disease subsequent to a time in issue, may evidence its prior existence.

In *R. v. Clarence* (1891) the prisoner was indicted for 'unlawfully and maliciously inflicting grievous bodily harm' upon his wife, and with 'an assault' upon her 'occasioning actual bodily harm' (to wit, infection with gonorrhoea), under sections 20 and 47 respectively of the Offences against the Person Act, 1860. In delivering the judgement of the majority in the Court of Crown Cases Reserved, Baron Pollock said: 'In *R. v. Bennett* (1866) an uncle was indicted for an indecent assault upon his niece, he being diseased, and she ignorant of the fact. It was

held by Willes, J., that the prisoner could be properly convicted, and in his summing-up that learned judge said, "An assault is within the rule that fraud vitiates consent, and therefore if the prisoner, knowing that he had a foul disease, induced his niece to sleep with him, intending to possess her, and infected her, she being ignorant of his condition, any consent which she may have given would be vitiated, and the prisoner would be guilty of an indecent assault." This case was followed by *R. v. Sinclair* (1867), in which the prisoner, being diseased, had connexion with a girl who, being ignorant of the fact, consented. As far as I can discover, these are the only decisions which have any material bearing upon the case now before us. They are not binding upon this Court, and they have been much questioned in the civil case in Ireland of *Hegarty v. Shine* (1878). As at present advised, I see great difficulty in adopting them in their entirety. If the reasoning upon which they are founded be sound, I should have thought that the offence of which the prisoners were guilty was not an assault, but rape. Without, however, further argument and consideration, I am not prepared to say that they should be overruled, especially as in cases of a similar kind, which may well arise, they are undoubtedly important and useful in the administration of the criminal law; but I cannot assent to the proposition that there is any true analogy between the case of a man who does an act which, in the absence of consent, amounts to an indecent assault upon his niece, or any woman other than his wife, and the case of a man having connexion with his wife.'

In Denmark and in Norway it is a criminal act to infect another person with venereal disease. In the Canada 'Lancet' (1897) a case is recorded where five years' imprisonment was the punishment inflicted on a man who infected with syphilis a woman whom he had ravished. At the Staffordshire Winter Assizes (March 6), 1908, a man was sentenced for committing an indecent assault upon and infecting with venereal disease a girl of fourteen. In *Hegarty v. Shine*, referred to above, Chief Justice May, while considering the extent of the consent

given, pertinently asked : ‘ Suppose that the operator used in the operation a poisoned instrument ? ’ In the same judgement it was, however, declared that ‘ Courts of justice no more exist to provide a remedy for the consequences of immoral or illegal acts and contracts than to aid or enforce those acts or contracts themselves.’

Where a woman substantiates her allegation of having been ravished by her infection with venereal disease, she must show that previous to the alleged rape she was free from the disorder, that the period of incubation tallies with her dates, and that the alleged assailant was, at the time of the offence charged against him, suffering from the same disease which the woman herself presents.

The question may be raised as to how far the existence of a dangerous or loathsome disease can be pleaded in justification of a breach of the contract and promise to marry. In 1907 the Supreme Court of Washington decided that a breach of promise of marriage on account of tuberculous disease in the fiancée was justifiable, even although the matrimonial engagement was entered into with a mutual knowledge of her condition (*Grover v. Zook*). This decision (U.S.A.) carries the legal standpoint of these contracts further than in any previously reported case ; while inflicting hardship upon the afflicted party it is doubtless directed towards the protection of the public health. In 1886 a somewhat similar case was decided in the Supreme Court of Pennsylvania : it was allowed as a valid defence to an action for breach of promise to marry that the plaintiff was incapable of performing the physical functions of matrimony, which disability she had agreed to have removed by a surgical operation before the wedding-day, but had failed to take steps so to do (*Gruig v. Lerch*). Our own courts would not accept such defences where such a simple contract had been entered into by interested parties : Mr. Justice Matthew in one such case is reported to have said, ‘ Love is not a necessary element in a breach of promise case ’ ; and Mr. Justice Vaughan Williams stated that bodily illness, whilst possibly being a plea against specific per-

formance of the matrimonial contract, was no defence against damages—for the fiancée may, as did Lady Teazle, ‘like to be a widow.’ Altered views of zymotic pathology may render insecure the leading decision in our own legal records as to disease in the defendant being set up as a defence to an action on a broken contract to marry; in *Hall v. Wright* (1859) failure of health, owing to pulmonary tuberculosis, was vainly pleaded as an excuse from a man who declined to fulfil his promise to wed. The principles which obtain in such an alleged impossibility or undesirability of completing the matrimonial agreement may be analysed from the point of view of the defendant to the action. Since one of the primary and essential objects of marriage is, in the words of the Book of Common Prayer, ‘For the procreation of children,’ such an objective may become impossible or its consummation very dangerous to the health of either party should the defendant’s physical condition have been materially affected by disease. On the other hand, the disease may make the matrimonial functions impossible of performance or dangerous to one party only to the contract. In the latter case several alternatives present themselves. The existence of disease may have been known to the defendant at the time when the contract to marry was entered into, it being reasonably thought that the malady was curable; the recent decision cited above shows that logic compels the recognition of the validity of such a defence by courts which would protect the defendant whose physical disease is only discovered subsequently to the marriage engagement. Should there be no reasonable ground to think that the position will be altered before the marriage ceremony is performed, as, for instance, where an already married man ‘proposes’ to a spinster or to a widow, the defence of the obvious possibility of redeeming his promise is futile. There remain the cases where the disease first appears subsequently to the time at which the contract was entered into; here the defendant may be disabled owing to his own fault, as where he has contracted gonorrhoea or syphilis, or he may have become infected innocently, as with pulmonary tuberculosis. In the

former case no defence could be allowed on that account. In the latter case the English courts likewise decline to allow the supervening pathological circumstance to excuse the fulfilment of the promise, for it is held that the performance is not necessarily impossible, and even if the full consummation of matrimony was impossible the plaintiff could still enjoy the social position which would result from the intended marriage alliance. The cautious wooer, if not going so far as to mark his letters 'Without prejudice', would insert in his written proposal a reservation in case of a change of bodily health in either party, or perhaps would suggest that a satisfactory medical certificate should be produced by each party before the wedding-day was named. A case sometimes cited as bearing on the general issue above set out is *Baird v. Graham* (1852, 14 Dunlop Sc. 615), where it was held that a master is responsible for knowledge of a disease existing in one of his horses. 'The decision in *Hall v. Wright*,' says Sir Frederick Pollock, 'can only be reviewed by a court of ultimate appeal; but it is so much against the tendency of the later cases that it is now of little or no authority beyond the point actually decided, which for the obvious reasons indicated in some of the judgements is not at all likely to recur.' *

DEFAMATION

Professional Secrecy and Defamation of Character. At the outset, in discussing the possibility of allegations of defaming the characters of patients in this connexion, it must be reasserted, at the risk of enforcing the obvious, that the correctness of the diagnosis is all-important: the truth of the statement of alleged fact may have to be substantiated and proved. It is wise habitually to use the terms 'specific disease' and 'urethritis' in preference to syphilis and gonorrhoea and, in writing, to prefer such symbols as Σ and \odot respectively. In signing medical certificates in which the nature of the malady has to be stated, it is wise to preface the diagnosis given with 'in my opinion';

* See also the case *Beans v. Denny* (Supreme Court of Iowa), reported in the *Journal of the American Medical Association* (1909, vol. i, p. 729).

such certificates should be handed unsealed to the patient, and not to third parties without the patient's definite consent. In all dealings it must be remembered that specific infection is not always venereal in origin.

The legal rule that a definite pecuniary loss must be proved successfully to uphold an action for slander, that is, alleged defamation by mere word of mouth, is probed by several exceptions, some of which are especially pertinent to members of the medical profession. Thus, the Slander of Women Act, 1891 (section 1), runs: 'Words spoken and published which impute unchastity or adultery to any woman or girl shall not require special damage to render them actionable.' Again, if there be a *viva voce* imputation that a person is suffering from a present contagious disease of a definite kind, the person defamed is not bound to show that actual financial loss has been the result. Thus, Blackstone (1794) cites the allegation of plague, leprosy, and *lues venerea* as being actionable, because of the connoted imputation; to impute the existence of a past infection would not come under the exception, and special damage would have to be proved before the defamation could be worth suing upon (*Carslake v. Mapledoram*, 1788, and *Bloodworth v. Gray*, 1844). 'He has the pox' was assumed to imply variola, as the context did not infer the presence of syphilis (*James v. Rutlech*, 1599). In 1902 a barmaid secured £75 damages from a medical man who had made allegations of the above kind against her (*Leeds Spring Assizes, Guy v. Green*).

The medical practitioner may be either wrong or wronged in these matters; he may passively be defamed or he may himself—often, perhaps, unwittingly—be the active defamer. It is this latter aspect which demands as a practical rider a consideration of the great questions: What are the proper limits of professional secrecy and confidence? What is the extent of the privilege, if any, allowed by the law in cases involving this factor? There are occasionally cases in which the medical practitioner feels it a public and a moral duty to say something about somebody and to remove the silencing finger from his lips; there is at

times some degree of foundation of reasonable self-interest or of ethical duty to support what has been stated by the person sued for the alleged defamation of character.

First, then, in what cases is a medical practitioner, as such, likely to be defamed and so injured professionally? Secondly, into what pitfalls may he project himself in referring to his patients or to his brother practitioners?

1. There are not many recorded cases in which the medical practitioner has been defamed. Cases might arise from allegations of negligent or wrongful diagnosis or treatment, or insufficient care in the thorough disinfection of instruments used, or in the omission to inform a patient of the condition of another patient when such persons are known to contemplate a close personal relationship.

2. The second possibility is of wider scope, and affords many illustrative instances of forensic proceedings. How may a medical practitioner by his own statements find himself set down as the defendant in an action for defamation of character? Mr. George Meredith, describing in one of his works a solicitor, said of him: 'A very worthy old gentleman he was, with a remarkable store of anecdotes of his patrons, very discreetly told, for you never heard a name from him.' This is the kind of reputation which all professional men—medical men and ministers of religion, as well as lawyers—should strive to attain. The professions in practice are based largely upon purely confidential relationships in which it is mutually recognized that open confession to the skilled listener is good for the body, the mind, and the estate respectively of the one confessing. The fact is that many of the transactions which result from such professional relations need the fullest disclosure of the patron's secrets—he must reveal his business and his bosom. For instance, the connotation of the phrase, 'a family doctor,' may be recalled. It can well be appreciated on such grounds alone what an excellent, if dangerous source of apposite anecdote the professional relations may be, and in fact are. Hence the golden rule of silence must constantly be observed by medical practitioners: to adapt the words of

Junius (1770), a medical adviser must be 'the sole depositary of his patient's secrets, which shall perish with him'. Indeed it is a commendable and growing custom for medical practitioners to direct, in their last wills, the immediate destruction, unread, of all private case-notes. The medical faculty, like the other professions, has formed a standard code of etiquette binding upon its members, albeit without legal sanction. One of the most ancient items of this medical code is instanced by the oath of Hippocrates, pledging secrecy with respect to all knowledge gained by a medical adviser as such : *I swear . . . whatever in connexion with my professional practice, or not in connexion with it, I see and hear in the life of men, which ought not to be spoken of abroad, I will not divulge, affirming that all such facts should be kept secret. While I continue to keep this oath unviolated may I enjoy life and practise my art respected by all men in all times ; but should I trespass or violate this oath may the reverse be my lot.* Although such a declaration is no longer formally taken in England, its sense is so emphatically maintained by the profession as a whole that the opinion of Thomas Vicary in 1517 still holds : surgeons 'must be as privie and as secrete as any Confessor, of all thinges that they shal eyther heare or see in the house of their Pacient'. Notwithstanding this ancient and pious usage in the profession the only legal penalty incurred by discussing the nature of the ailments of others is the risk that thereby the latter's characters may be defamed and the obnoxious proceedings will then become subject to the law of the land. Associated with this implied pledge of secrecy, there are definite occasions when the confidence of a patient is, as a matter of fact, liable to be disclosed more or less publicly, with impunity. There are the cases where a medical man is called in to supersede a previous inefficient medical adviser ; and, on the other hand, there are occasions when clinical facts must be revealed on the principle *se defendendo* ; the communications of partners and of near relatives also raise practical points ; finally, this 'confidence' claimed by medical men is not recognized as binding in a court of law. The motives leading to the disclosure of the results of

professional transactions may be either *private and personal* or *public and forensic*.

(a) The private and personal motives which may lead to the exceptional revelation of medical facts gained by a medical adviser, as such, are several ; in very few cases are they regarded as justifiable. For their justification it is premised that their publication is quite devoid of any exhibition of malice, actual or implied. Thus, if the safety and health of a member of a medical practitioner's own family were endangered by an intended alliance with one known professionally to be suffering secretly from 'a bad disorder', the magnitude of the moral pressure which would be exerted by this knowledge would be sufficient ground to justify a disclosure of the state of affairs to the party personally to be affected ; this action should, however, only be taken after due precaution. In the case where a near relative was in danger 'the plea of necessity' would probably be sufficient ; where a friend merely was likely to be implicated it might be enough to threaten the infected person with a full disclosure of the facts if the intended marriage was arranged before the disease was cured. When 'fishing inquiries' were being made Brouardel advised medical men to stop them peremptorily at the outset. Fournier, in 1828, declined to state the facts concerning a syphilitic husband ; he was supported on appeal (Code Pénal, art. 378). Fournier is said to have been in the habit of advising parents, who came to interrogate concerning suspected venereal disease on these occasions, to bring the intended husband for an interview with the family medical adviser ; Brouardel suggested that the parent should be advised to see that the prospective son-in-law was sufficiently insured, thus conveying a hint which not infrequently resulted in a full explanation by the person most concerned. Pinard urged that, as a last resource, the facts should be disclosed to the bride's family. The problem is discussed in drama in M. Brioux' *Les Avariées*.* The duty of medical reticence may be questioned when a conscienceless blackguard is being dealt with, who will

* See also Dr. Queirel's *Leçons de Clinique Obstétrique* (Paris, 1908).

not heed the medical advice and exhortation, prompted by humanity, to postpone matrimony until all danger of possible infection is past.

A medical practitioner may feel bound in certain other social dilemmas to infringe the privilege of non-disclosure. Thus, he may know that the physical condition of a callous and indifferent patient is dangerous to his daily associates, e.g. in the use of a common lavatory or of feeding utensils ; or in the case of a glass-blower or milk-carrier suffering from sores specific in origin. The only advice which can be given is that in each instance the lesser of the two evils, of silence or of speech, must be chosen, when all the facts of the special case have been balanced. Sometimes a judicious note to the employer, without indicating the actual offender, will suffice ; in such cases the sufferer may be made to cease work but his financial condition will be protected. When it is a matter of certifying the present health of or the cause of the death of a person, it may be presumed that the parties requesting such a voluntary document realize that it will technically be published. In the latter case district registrars of deaths have been known to reject such a medical cause of death as 'marasmus', having reason to believe that 'congenital syphilis' was the real fatal cause ; this may be more the custom when the notification of still-births is universal. In 1904 it was held to be libellous to publish an advertisement stating that a named person had been cured of a certain disease by a certain drug. In reporting clinical cases to a learned society or in the professional press, the photograph, the initials, and often the age of the patient should be judiciously withheld, for fear of revealing his identity to curious neighbours who may gain access to the clinical publication, perhaps in a public library.

An infant, under the age of 21 years, may get into physical distress and privately apply to a medical adviser for advice and treatment ; subsequently he may repudiate the account rendered for professional care. Can the parents or guardians be applied to for settlement ? If he so acts, the medical man may be accused of defaming the character of his youthful patient,

although, as a defence, it would be urged that such medical aid is a 'necessary' within the meaning of the Act, and the infant himself is held liable for any such debt which he may contract and such liability may ultimately imply the publicity of the County Court. As a matter of safe practice, persons under the control of others should not, if possible, be treated unless the latter know of it; this precaution applies particularly where a physical examination of a child is to be made.

(b) There are occasions when public or forensic motives may lead to the disclosure of otherwise confidential clinical information; such 'discoveries' are sanctioned, in law, on the all-sufficient ground of public policy absolutely, that is to say, the question of malice does not affect the matter. This forensic view often cannot be seen from the medical practitioner's standpoint, for his wish is at every opportunity to screen the patient and his private life and ills. Jeremy Bentham used to insist that legal officials and public authorities are apt to place civil duties foremost, riding rough-shod over human susceptibilities. Arguing from analogy, in other professions it is held that communications between a client or a witness and the legal adviser or advocate, and probably between a clergyman and a member of his flock, are recognized in law as being absolutely privileged and their publication cannot be insisted on. Arguing from the customs of other legal systems, in France (Code Pénal, art. 378), in Germany, and in many of the United States of North America (e.g. New York Code, art. 834), the relations between the medical adviser and the patient advised are regarded as of an absolutely confidential nature; in Scotland, secrecy is a condition of the medical contract, and any breach may be held a relevant ground for an action for damages (1851); among Scotch medical graduates a pledge of professional secrecy obtains; since the Act of 1885 secrecy has been enforced in civil cases in New Zealand. This privilege of medical confidence has been objected to as likely to hinder justice being done in such practical matters as claims arising under policies of life insurance, from injuries the result of malice or neglect, and in mental and matrimonial disputes;

it has been ruled, however, in New York, that a medical adviser may testify with impunity as to his professional engagement and the number of his visits and clinical examinations, his prescriptions and his operations, and, if there is any objection raised to a description of them, he may testify as to his opinion of their value.

In his semi-public capacity a medical practitioner may be called upon either to act as an *informer* or to give evidence under oath as a witness in legal proceedings. The question as to how far such a person should volunteer to act as an informer when his patients decline to follow his advice has been referred to above; cases with associations distinctively criminal are rare in this connexion, hence an information to the Public Prosecutor will very seldom be suggested. Medical men may be compelled by statute to notify, under penalty, the existence of such cases of syphilis as come under their professional care, as when the Contagious Diseases Acts were in force in certain naval and military towns; in this case, of course, the information could not be said to be volunteered. Where medical certificates are demanded in the Services it may be necessary to notify similarly such facts to recognized authorities (as in the London Fire Brigade case, *Still v. Morris*, 1900). Many hold that a known prostitute suffering from venereal disorder should be subject to notification and segregation, and further that, as is the practice in Denmark, all those suffering from syphilis should be treated at the public charge.

Passing from the cases where a medical practitioner may be expected upon grounds of public policy to afford information to third parties as to the health of patients, there is the final class of cases where the publication of medical facts, otherwise recognized to be confidential, is compulsory, and as such, provided they are material to the issue under consideration, is absolutely privileged, so that not even proof of a special bias in the publication made is sufficient to render the medical adviser liable to conviction for defamation of character. These are the cases of medical practitioners under examination as skilled witnesses of

fact in legal proceedings, including of course those of the Coroner's Court. It was decided in 1905 by the House of Lords, upon appeal, that this privilege against legal action extends to a medical witness making statements to the solicitor preparing the 'proof' of his evidence (*Watson v. McEwan*).

The cases in which the 'discovery' of medical documents or information, prepared or obtained by a professional adviser, may be objected to upon the ground that such disclosures would be breaches of professional confidence, arise chiefly in connexion with reports by medical men for railway companies or insurance offices: in the former case, since 1859, it has been held that the claimant cannot call for an inspection of such a report unless he was clinically examined in the ordinary routine course, as after an accident; in the latter case, since 1851, the medical report, if demanded, must be produced. It is not generally known, however, that there is a central clearing-house through which pass the names of all applicants for insurance policies amounting to more than one hundred pounds.

Medical evidence is only excluded on the ground of public policy when subject to certain rules of law, as communications between husband and wife during coverture, and unnecessary disclosure of matters indecent or offensive to public morality or injurious to the feelings of third persons. It may be noted here that the exposure in public places of certain illustrations of syphilitic conditions ranks with the public exhibition of indecent postcards, and to that extent can be prohibited by the police. It is, of course, a forensic axiom that medical witnesses may decline absolutely to reply to any question which would in any way incriminate or penalize themselves, this being the general rule with all classes of witnesses, upon the principle: *Nemo tenetur prodere seipsum*. Occasionally, by the strict practice of what is the recognized professional etiquette, an action for damages, rightfully due, may be forfeited: there is an insurance case recorded where a medical man declined to mention in court the name of the patient (and thus to disclose his identity) who had infected his wounded finger with syphilis; on that account

he failed in his action (*St. Clair Gray v. Northern Accident Insurance Company*, 1896).

A medical witness in such a predicament should either hand a written statement directly to the president of the court or should refuse to give evidence on the matter, accepting the consequences of 'contempt of court' if his inaction in this particular was so deemed to be. In any event, the objection to disclose medical facts will be allowed as proper, even if the medical witness is instructed by the court to consider himself compelled against his wish. It would be distinctly advantageous to the profession if definite authoritative rulings and not mere *obiter dicta* were available in this matter of 'discretion' and 'privilege'. In all cases, it is a matter for the judge to decide as to the validity of the objection of a medical witness under oath to disclose certain clinical facts within his knowledge. On these matters should be consulted (*a*) Counsel's opinion obtained by the Royal College of Physicians of London in 1896, and (*b*) the Proceedings of the General Medical Council, 1899, p. 199.

Stanley B. Atkinson.

SYPHILIS AND LIFE ASSURANCE

BY

E. M. BROCKBANK, M.D., F.R.C.P.

CHAPTER XVI

EVIDENCE DERIVED FROM CLINICAL AND PATHOLOGICAL SOURCES

INTRODUCTORY

THE question of the value for assurance purposes of a proposer who has had syphilis is an important one, for it is universally acknowledged that such a man is liable to several diseases which one who has not had syphilis is exempt from. The importance of the question is further increased when we know that some authorities state that 20 per cent. of all male assurance proposals are from syphilitics. But although all observers agree that syphilitic infection is followed by certain sequelae, there is divergence of opinion as to the number, variety, and danger of these sequelae, and, consequently, when applied to assurance work, there are differences of opinion amongst experts as to what is the extra risk for assurance purposes of a syphilitic proposer as compared with one who has not had syphilis.

It will be the object of this section of the 'System of Syphilis' to consider the whole question, and to review the facts which ought to be known to the assurance experts when they are dealing with proposals from syphilitic men. It may be said here that nearly all the facts and figures of this article refer to males only, female proposals being few, and the risk from syphilis in a woman of the insuring classes being even less than for a man.

The information which is necessary for appraising syphilitic risks is chiefly drawn from two sources—medical and actuarial, or from clinical and pathological observation and from the experiences of assurance companies in these risks.

We will consider the medical side of the question in the first

instance, then the actuarial, and finally, after having reviewed the customs of different assurance experts in dealing with syphilitic risks, draw some general conclusions.

Whilst there is no justification whatever for the old saying that 'syphilis never kills', for obvious reasons this disease is rarely, if ever, given as a cause of death on a certificate, and in inquiring into its effect on the duration of life, it is necessary to consider carefully what are the various diseases which can be registered without offence, and yet, at the same time, indicate distinctly to the medical mind the real primary cause of death.

Present-day observations have considerably widened our knowledge of the subject, and show that tertiary syphilis and the so-called quaternary syphilis, or the parasyphilides, involve more of the viscera than was believed to be the case even ten years ago. It will therefore be necessary to consider carefully (1) what are the possible results of syphilitic infection, and (2) the probability of their development; (3) the danger to life of these sequelæ of syphilis; and (4), a very important point for the actuarial requirements, the age at which death is likely to occur from them. It will also be of use to have some knowledge of the extent to which syphilis prevails amongst the assuring classes, and the age at which it is usually contracted.

THE FREQUENCY OF THE OCCURRENCE OF VENEREAL DISEASE IN THE POPULATION GENERALLY

Information on this point is not easily obtained, and, though interesting, it is of but minor value to an actuary. Nor is it of much value to the medical examiner to know whether a small or large percentage of proposers are syphilitic; he ought always to be wide awake in his search for indications of the infection, especially as many syphilitic applicants do not state in their proposal forms that they have had syphilis, either because they would rather forget, or have actually forgotten, such an incident in their previous medical history. Some also may have had a mild dose of the poison without knowing it. But all facts more or less remotely bearing on the question of syphilis are valuable

as broadening the premises from which conclusions are deduced, and accordingly the few figures which I have been able to find will be referred to.

Syphilis is much more common among men than women—three to eight times as common, according to different observers.

In men it is more common in the better classes than in the lower classes; and of the latter, the town population is much more generally affected than the country dwellers.

On the other hand, the women of the better classes are relatively less liable to infection than are those of the town population.

In Copenhagen, on an average, 16–20 per cent. of young men between 20 and 30 years of age are infected with venereal disease, that is, one in every five or six. One in every eight has gonorrhoea, and one in every fifty-five has syphilis (Ehlers).

In Christiania the prevalence of these affections is much the same: 13.1 per cent. for all venereal diseases, and 3.2 per cent. for syphilis.

Blaschko states that, in Berlin, 200 of every 1,000 young men between 20 and 30 yearly contract gonorrhoea, and four out of every 1,000 contract syphilis.

A young man will contract gonorrhoea once in every five years of bachelorhood, and after eight to ten years every fifth bachelor will have been infected with syphilis.

In other words, every man who is not married until he reaches the age of 30 will have had gonorrhoea twice, and every fourth or fifth syphilis.

Erb states that in 10,000 cases of all varieties of disease in his practice, excluding tabes, in men of the better class, 21.57 per cent. had had syphilis. Including tabetics, the percentage would have been higher, because he finds 89 per cent. of these patients have had syphilis. He believes that 12 per cent. of the population of Berlin are syphilitic.

Audry states that 18 per cent. of the lower classes of Toulouse are syphilitic.

I have been unable to find any similar figures for England. the nearest being Fournier's opinion that there is less syphilis

in London than in Paris, for which he estimates the percentage at 15. Dr. Byrom Bramwell thinks that 20 per cent. is too high an estimate for the number of proposers for assurance who have had syphilis.

The returns from asylums, although they are valuable as indicating the frequency of syphilis as a cause of mental disease, are not of any wider significance.

Information as to the frequency of syphilis in America has not been forthcoming.

As far as my own experience of assurance examinations amongst the mercantile classes goes, I consider that it is overstating the case to say that in English assurance work one proposer in every five, or even in every ten, has had syphilis. Certainly I have been unable to get any such history, or of gonorrhoea, from this latter proportion of proposers, and this with a special intention of obtaining such information, or in finding evidence, by judicious questioning and by careful examination, of past venereal disease. In my last 700 examinations of applicants for assurance, one man had gonorrhoea when he called; another told me he had had syphilis, but from his account and from the details of treatment which he gave me, I doubted the correctness of the diagnosis; and one man had specific ulceration of the throat at the time of examination. A few others, but certainly not 10 per cent., gave a history of past gonorrhoea or syphilis, but I found no indications of visceral lesions in any of these 700 applicants.

AGE OF CONTRACTION OF SYPHILIS

Fournier, from an experience of 11,000 cases of syphilis (10,000 males and 1,000 females) acquired by sexual contact only, found that the disease is contracted most frequently between the 20th and 26th years in men, the maximum being attained in the 23rd year. In women syphilis is contracted most frequently between the 18th and 21st years, with maximum risk at the 20th year.

Eight per cent. of men and 20 per cent. of women who contract syphilis are infected before the 20th year.

Whilst these broad statements are useful, the age of contraction of the disease must be definitely ascertained from each proposer who acknowledges infection.

FREQUENCY OF THE APPEARANCE OF TYPICAL TERTIARY LESIONS IN SYPHILITICS

M. K. Grön, collecting information from various sources, found that, in a total of 40,228 cases of syphilis, 4,727 developed tertiary syphilis, i.e. 11·75 per cent. Audry, from the Toulouse clinique, found 16·8 per cent. of tertiaries to occur; and Mathes, at Jena, found 19·4 per cent.

Other observers have published their experiences as follows :—

Rollet of Lyons : 5 per cent. amongst private patients who have been well treated; 15 per cent. amongst hospital patients less thoroughly treated.

Diday, Lyons : 12 per cent.

Mauriac, Paris : not less than 5 or more than 20 per cent.

Raff : 9 per cent.

Haslund, Copenhagen : 12·4 per cent. hospital.

Ehlers (6,816 cases): not less than 12·4 or more than 22 per cent. hospital.

Neumann and Vajda, Vienna : 6·82 per cent.

Marschalko, Breslau : 7·4 per cent.

Dr. Heron states that if disaster involve a community it may affect the health of a large number of well-to-do persons. People with a syphilitic history, who for years have been apparently healthy and are suddenly poverty-stricken, may suddenly show signs of syphilis which had been latent for years. Mr. Buxton Shillitoe has also seen, in many cases, syphilis, in severe form, recrudescent in patients in time of severe commercial strain and distress.

SYPHILIS AS A CAUSE OF DEATH

On going through the causes of death of 4,013 hospital patients, Audry found that thirty-four were due directly and fifty-seven indirectly to syphilis. Assuming that 20 per cent. (802) of the total number of patients had had syphilis, a death-rate of 91

in this 802 would be 11·3 per cent. He thinks this is a much more likely figure than Blaschko's of 35 per cent. amongst the assured.

Dr. Byrom Bramwell believes that 7·5 per cent. of syphilitics die directly from the effects of the poison.

Dr. Parkes Weber attributed death to syphilis in 3·6 per cent. of 500 general deaths amongst the assured, and this, assuming that 20 per cent. of the 500 had had syphilis, makes 18 per cent. of deaths of syphilitics due to syphilis.

The average age at death of 87 hospital patients at Manchester Royal Infirmary in whom syphilitic lesions were found at the autopsy was 39 years. The males numbered 62, with an average age of 38 years, and the females 25, with an average age of 40·2 years. Syphilis was probably directly responsible for death in at least 40 of these cases.

DISEASES ATTRIBUTED TO SYPHILIS

The diseases which clinical and pathological experience attribute to syphilis are as follows :—

Diseases of the Central Nervous System :

Locomotor ataxia.

General paralysis.

Meningitis.

New growths of the brain or spinal cord.

Vascular Lesions :

Apoplexy before 50, and especially before 40 years of age.

Cerebral softening—Endarteritis obliterans.

Pulmonary Organs :

Tuberculosis in the early months or years after infection with syphilis.

Diseases of the Circulatory System.

Arteritis.

Aneurysm.

Angina pectoris before 40 or even 50.

Cardio-vascular sclerosis.

Myocarditis	} before 40 or even 50.
Coronary arteritis	

Diseases of other viscera, especially of the *liver* and the *kidneys*.

I do not propose to argue fully the case for and against the views that syphilis has a most important effect in predisposing the system to any or all of these various diseases in later life, or that it actually causes these diseases. For such an argument other sections in this System must be consulted. I shall content myself with epitomizing the evidence which bears on the questions at issue.

NERVOUS SYSTEM

Several important lesions of the central nervous system may result from syphilitic infection. In Fournier's experience of the systems of the body, the nervous system is most frequently affected with tertiary lesions. Thus, in 4,400 cases of tertiary syphilis in Fournier's practice, there were 1,851 cases of nerve lesions, 628 being tabes, 45 cerebro-spinal tabes, 758 syphilitic inflammation of the brain, 136 syphilitic inflammation of the spinal cord, 86 general paralysis. Amongst other important lesions were affections of the lungs, 23; heart, 7; arteries, 15.

TABES DORSALIS AND GENERAL PARALYSIS OF THE INSANE

The most important and frequent of the later manifestations of syphilis in the nervous system are those of tabes and general paralysis of the insane. These diseases, so-called parasyphilides, are very closely allied to each other at certain stages of their appearance, but it will be convenient to discuss them separately, allowing overlapping to take place when necessary.

Tabes Dorsalis. Although Duchenne, in 1859, and other writers had noticed that some tabetics had been previously affected with syphilis, Fournier was the first, in 1875, to maintain that such a history was to be obtained in a large number of his cases of tabes.

Dr. Ferrier relates some very interesting evidence on the subject.

Erb, who, when Fournier first promulgated his views on the syphilitic origin of tabes, strenuously opposed the theory, is now the most eminent advocate of it. He states that, amongst 1,100

cases of tabes in his own practice among men of the better class, 89·45 per cent. had had chancre or syphilis, and only 10·54 per cent. had not been ostensibly infected. But of these, in only 3 per cent. was it impossible to find any ground for suspecting an antecedent syphilitic infection.

As a contrast, Erb took 10,000 cases in men of the better class of all varieties of disease, excluding tabes. Of these, only 21·5 per cent. had had syphilis, that is to say that syphilis was found 4·5 times more frequently among tabetics than among other patients.

Among fifteen tabetic women of the better class, at least 86·7 per cent., and probably 93·3 per cent., had been infected. Similar investigations among 158 tabetic men of the lower orders gave a somewhat lower percentage of antecedent syphilis, namely 77·2 per cent. Taken altogether, this inquiry among 1,321 cases of tabes, namely 1,100 men of the better class, gives 89·5 per cent. infected; among 158 men of the lower class, 77·2 per cent.; and among 63 women, 80 per cent., as probably infected. Essentially the same is true of general paralysis.

‘The classes who sow wild oats most freely are those who reap tabes most abundantly. Townspeople furnish more cases than those who live in the country; and the great centres of population more than the smaller. Tabes and general paralysis are rare among priests, and of these affect only such as have had syphilis or exposed themselves to it’ (Ferrier).

Tabes is less common among women of the better than among those of the lower classes.

It seems very probable, therefore, that tabes and general paralysis can only develop in those who have at one time been infected with syphilis, although it is also probable that some other cause not definitely known may be contributory. The failure to obtain a syphilitic history in the 10–15 per cent. of cases is not difficult to understand, in view of the facts that Hirschl could only obtain a certain history of syphilis in 54 per cent., and a possible history in 9·5 per cent. more, of indubitable gummatous affections of syphilitic origin. In 36·6 per cent. no evidence of syphilis other than the patients’ actual state was forthcoming (Ferrier).

Similarly Pernet could only get a definite history of syphilis in 80 per cent. of cases of undoubted syphilitic affections of the skin.

Viannay, in hospital syphilitic patients, could not obtain any history of infection in 52 of 100 cases.

With syphilitic women the history is negative in nearly all instances.

Dr. Ferrier concludes: 'One may say with justice that the syphilitic origin of tabes and general paralysis is statistically just as well proved as that of gummatous affections of the skin.'

Dr. Mott also refers to some interesting experiences of continental observers:—

Gilles de la Tourette and others have recorded a series of cases of nervous disease following infection from the same woman. Babinski reports the case of two students who were infected the same day by the same woman; both died fifteen years later of general paralysis; these students were, however, related. Marie and Bernhard relate the instance of two men who were infected from the same source, and ten years later suffered from tabes. Erb narrates the instance of four patients infected by the same woman, who later became the subjects of either tabes or general paralysis, whilst a fifth who had connexion with the woman, but who was not infected, did not suffer from any disease later. Probably the most striking example supporting the theory of a special neurotoxic virus has been afforded by Brosius, who relates that seven glass-blowers suffered with chancre of the lip, and out of five who ten years later came under observation, four suffered either from tabes or general paralysis.

Apart from juvenile tabes, which is always syphilitic, hereditary or acquired, tabes occurs most commonly among men of from 30 to 40 years of age, and on the average from seven to ten years after primary syphilitic infection. There are, however, exceptions to this rule, and Ferrier has seen it develop in a man of 70, some forty or fifty years after infection with syphilis; and there is a case on record of a man of 74 becoming tabetic after infection at the age of 70 (Ferrier).

General paralysis and tabes frequently develop in later life in persons who had a mild syphilitic infection, and who were probably, on this account, submitted to only a mild course of treatment.

Neisser, from an examination of 540 cases of tabes, found that more than half the cases had not been treated at all, more

than 40 per cent. had undergone only one course of treatment or a very irregular treatment, and only 5 per cent. had been properly dealt with.

Paul Cohn similarly found in 117 cases of tabes that eighty-nine had no mercurial treatment, and of the remaining twenty-eight only three or four had undergone repeated mercurial cures.

Dr. Byrom Bramwell has analysed his notes of 263 cases of locomotor ataxia which he has himself seen in practice, and amongst other points he found that 209 of the patients (82.6 per cent.) had suffered from some form of venereal disease, whether hard or soft sores or gonorrhoea. It was probable that many of the other patients who denied syphilis had really been infected with it at some time of their lives. In 253 of the cases there was a definite note about syphilis; 155, or 65.2 per cent., admitted syphilis; in 4.7 more, from the family history it was practically certain that the patient had had syphilis; in 6.3 per cent. there was some doubt; and 27.6 per cent. denied syphilis.

Several of the cases which had acknowledged having had syphilis had been treated very thoroughly for long periods of time with mercury, a fact which shows that such treatment does not always prevent the subsequent development of tabes.

The length of time between the occurrence of the venereal sore and the first symptoms of tabes was investigated in a series of 141 cases :—

<i>Age.</i>	<i>No. of cases.</i>	<i>Per cent.</i>
Under 1 year	1	0.7
1-5 years	26	18.4
6-10 "	36	25.5
11-15 "	30	21.2
16-20 "	33	23.4
21-25 "	11	7.8
26-30 "	2	1.4
36-40 "	1	0.7
41-45 "	1	0.7
Total . .	141	99.8

From this table it is seen that in 63 of the 141 cases, or 44.6 per cent., the tabes developed within the first ten years after infection; in 78 cases, or 55.3 per cent., more than ten years after infection; in 63 cases, or 44.6 per cent., between ten

and twenty years after infection; and in 15 cases, or 10·6 per cent., more than twenty years after infection.

AGE AT ONSET IN 258 CASES OF TABES (Bramwell)

<i>Age.</i>	<i>No. of cases.</i>	<i>Per cent.</i>
From 20-30 years	37	14·3
„ 31-40 „	121	46·8
„ 41-50 „	70	27·0
„ 51-60 „	25	9·6
Above 60 „	5	1·9
Total . .	258	99·6

Thus before the age of 50 the disease commenced in 88·1 per cent. of the cases.

Dr. Byrom Bramwell has records of the total duration of tabes in 70 fatal cases, and finds the average duration to have been 8·2 years:—

Below 1 year	1 case	11-12 years	1 case
1-2 years	2 cases	12-13 „	5 cases
2-3 „	2 „	13-14 „	1 case
3-4 „	5 „	14-15 „	1 „
4-5 „	9 „	15-16 „	3 cases
5-6 „	8 „	16-17 „	1 case
6-7 „	3 „	17-18 „	3 cases
7-8 „	4 „	20-21 „	1 case
8-9 „	3 „	21-22 „	1 „
9-10 „	3 „	22-23 „	1 „
10-11 „	8 „	not stated	4 cases

The effect of tabes on longevity was calculated in 17 fatal cases. The expectation of life in these cases was diminished by 268·85 years, that is, an average of 15·81 years.

GENERAL PARALYSIS OF THE INSANE

The causation of general paralysis was referred to in part in discussing the etiology of tabes (vol. iii, p. 181, and vol. iv). Some further evidence is interesting. Asylum returns show the frequency of an antecedent history of syphilis in general paralytics. Thus Dr. Campbell at Rainhill Asylum reports:—

From 225 male and 57 female cases of the disease no history of any sort was obtainable in 76 and 9 instances respectively.

Of the 179 males, 62 per cent. were undoubtedly syphilitic.

24 „ „ were probably so.

13 „ „ gave no history of syphilis.

Of the 48 females, 37 per cent. were undoubtedly syphilitic.

60 „ „ were probably so.

2 „ „ gave no history of syphilis.

Fournier found that of 100 cases of general paralysis only five were treated thoroughly over a period of three to four years, fifteen for one and a half to two years, and eighty only imperfectly or for less than one year.

In his own practice Fournier found amongst 80 cases of general paralysis that 3 only had suffered from severe syphilis ; 8 were affected in a moderate way, and 69 but very slightly. Thus of 80 cases of general paralysis, 77 had syphilis only mildly. On the other hand, of 243 cases of severe syphilis, not a single one developed general paralysis.

Treatment has a great deal to do with the onset of the disease. Thus of 79 cases of general paralysis, in 44 the duration of the treatment did not extend longer than six to twelve months ; in 19 cases no longer than one year ; in 12 it was continued for two years, and in 4 cases for three years. Eighty per cent. of syphilitics who developed general paralysis had been insufficiently treated.

Fournier was able to give the time which elapsed between the date of infection and the definite diagnosis of general paralysis in 112 cases.

Towards the end of the third year	1 case
In the course of the fourth year	3 cases
„ „ „ sixth year	7 „
„ „ „ seventh year	8 „
„ „ „ eighth year	10 „
„ „ „ ninth year	10 „
„ „ „ tenth year	15 „
„ „ „ eleventh year	12 „
„ „ „ twelfth year	11 „
„ „ „ thirteenth year	5 „
„ „ „ fourteenth year	7 „
„ „ „ fifteenth year	6 „
„ „ „ sixteenth year	2 „
„ „ „ seventeenth year	2 „
„ „ „ eighteenth year	5 „
„ „ „ nineteenth year	3 „
„ „ „ twentieth year	2 „
„ „ „ twenty-third year	2 „
„ „ „ twenty-fourth year	1 case

112 cases

General paralysis, according to these figures, does not occur before the third year of infection, and Bramwell's earliest case was 2·5 years after infection.

The disease occurs most commonly between the sixth and the twelfth years, 65·4 per cent.

In the first two years	0·0	per cent.
From the third to the fifth	3·5	„
From the sixth to the twelfth	65·4	„
From the thirteenth to the twentieth	28·5	„
After the twentieth year	2·6	„

Hence about four-fifths of the cases occur from the sixth to the fifteenth year, with a maximum for the tenth (81 per cent.).

These figures were communicated by Fournier to the Paris Academy of Medicine in 1905, during a discussion on the relationship of general paralysis to syphilis. An abstract of the discussion is given in the 'Gazette des Hôpitaux' for 1905, and an epitome of it in Dr. C. F. Marshall's 'Syphilology and Venereal Disease'.

Joffroy, in the same discussion, stated his opinion that syphilis is not the efficient cause of general paralysis, and that the latter disease is not of the nature of a syphilitic affection. He accorded to syphilis only a predisposing action like alcohol, tobacco, over-eating, sexual excess, &c.

Raymond looks upon syphilis as a cause of general paralysis, but he also considers that a psycho-neuropathic heredity plays an important part in its development. Alcohol is another important cause of this disease, and of tabes and other nervous diseases.

Lancereaux used to look upon syphilis as a possible cause of general paralysis, but takes a different view now. He considers that the tertiary lesions of syphilis have characteristic features which differ widely from those of general paralysis, and he is guided in his opinion by the fact that antisiphilitic treatment has no effect on the disease. He argues that as there are general paralytics who have never had syphilis, the disease cannot be syphilitic. There are certainly syphilitic lesions which simulate general paralysis, but the characteristic lesion of the disease, diffuse periencephalitis, is absent in them.

Stanziale found in 100 cases of general paralysis a history of syphilis in 87 cases. In 70 the syphilis was evident, in the

other 17 there were only doubtful signs. In the 70 cases in which syphilis was evident there was no other cause in 32, but in the remaining 38 there were other etiological factors, especially neuropathic family history and alcoholism.

The average age at death in 52 cases of general paralysis in the experience of the Scottish Widows' Fund was 44 years; and of 14 cases in Dr. Bramwell's own practice, 40 years. Dr. Bramwell assumes that the average age of infection of these cases of general paralysis would be about the same as that for his cases of tabes, i.e. 27.2 years, and from this he calculates that the average diminution in the expectancy of life of these general paralytic cases would be about 20 years.

In Dr. Mott's experience, the average number of years intervening between the date of infection with syphilis and the onset of tabes or general paralysis is about ten, but the period may be much shorter or much longer.

Further information on parasyphilitic diseases of the nervous system will be found in other sections of this System.

The length of time the policies of those dying of general paralysis were in force in three assurance companies was as follows:—

<i>Age.</i>	<i>164 cases. Gotha Life Co.</i>	<i>101 cases. Austrian Phoenix.</i>	<i>86 cases. Victoria.</i>
Under 1 year .	5	3	17
From 1-5 years	33	20	29
„ 6-10 „	58	23	26
„ 11-15 „	39	16	10
„ 16-20 „	14	20	4
„ 20 and over	15	20-30 years 18	—
	—	30-40 „ 1	—
Total . .	164	101	86

OTHER CENTRAL NERVOUS SYSTEM LESIONS

The true tertiary syphilitic lesions of the nervous system are meningitis, gummata, and arteritis. They tend to develop earlier than the parasyphilitic diseases, and are therefore a much greater risk for assurance.

According to Fournier, tertiary lesions generally are most frequent in the second to the fourth years, after which they gradually become less common, and are rare after the twentieth

year. The maximum is in the third year, but cases are not uncommon in the first. They may also occur as late as fifty years after infection.

He gives the date of the onset of syphilitic hemiplegia, the most common and best defined type of cerebral syphilis, in 228 cases :—

1st	year	25 cases	16th	year	1 case
2nd	"	26 "	17th	"	3 cases
3rd	"	39 "	18th	"	1 case
4th	"	29 "	19th	"	5 cases
5th	"	20 "	20th	"	3 "
6th	"	10 "	21st	"	1 case
7th	"	13 "	22nd	"	5 cases
8th	"	4 "	23rd	"	3 "
9th	"	6 "	26th	"	2 "
10th	"	5 "	27th	"	1 case
11th	"	4 "	29th	"	1 "
12th	"	5 "	30th	"	2 cases
13th	"	3 "	33rd	"	1 case
14th	"	4 "	34th	"	1 "
15th	"	4 "	40th	"	1 "

Thus in cerebral syphilis two-thirds of the cases occur in the first six years of the disease, whilst in general paralysis about two-thirds of the cases occur between the sixth and twelfth years of the disease.

Naunyn analysed 325 cases of nerve syphilis, and found that the tertiary lesion developed in 20 per cent. of the cases during the first year after infection, in 34·7 per cent. from the second to the fifth years, in 24·9 per cent. from the sixth to the tenth years, in 10·7 per cent. from the eleventh to the fifteenth years, and in 20·2 per cent. after the sixteenth year.

Dr. Byrom Bramwell, in 107 cases (other than tabes and general paralysis), found that the tertiary lesion developed in 12·1 per cent. during the first year, in 40 per cent. during the first five years, and in 68 per cent. during the first ten years after infection. He explains the much greater frequency with which Naunyn found nervous lesions develop during the first year by the fact that most of the 325 cases were collected from medical literature, and that probably many of these were published specially on account of an early appearance of tertiary lesions. As a result of his examination of the subject, Bramwell concludes that the expectation of life in every case of tertiary syphilis is shortened by ten years.

Erb found that, in 22 cases of spinal syphilis in which the date of infection could be determined, 59 per cent. appeared during the first three years, and 82 per cent. during the first six years.

Sir William Gowers, in a series of 50 cases of cerebral endarteritis causing hemiplegia in patients between 25 and 45 years of age, found that 25 per cent. occurred within the first two years after infection, while the remainder were spread over the next twelve years.

Rumpf gives 23 per cent. of the cases of syphilitic affections of the membranes of the brain and spinal cord as occurring within the first year after infection; and Goldflam states that 72 per cent. of the cases of syphilitic disease of the spinal cord alone occur within two years of the infection.

Dr. W. A. Turner examined the dates of the onset of symptoms in 35 unselected cases of aphasia, hemiplegia, epileptiform convulsions, and oculomotor palsies met with in syphilitic subjects, and found that 9 occurred within the first three months of infection, and that in 16 cases symptoms ensued within the first five years; the remainder were observed between the sixth and the twentieth years.

Of 30 cases of brain syphilis which Dr. Mott had under his care with a sure history of the time of infection, one-half occurred within the first four years. Three cases occurred during the first year, 4 during the second year, 5 in the third year, and 3 in the fourth.

Other writers agree as to the early time of onset of brain syphilis.

SYPHILIS OF THE CIRCULATORY SYSTEM

Welch, in 1876, found disease of the aorta in 60 per cent. of post-mortem examinations on syphilitic subjects.

Continental observers have for many years maintained that syphilis produces a lesion in the arteries, especially in the aorta, which is quite different from that usually spoken of as atheroma. Döhle (1885 and 1895) described the changes as consisting of irregular nodular masses of a gummatous nature projecting on

the inner wall of the aorta, but arising originally in the tunica media, and hence called mesaortitis. Benda has pointed out that the medium and smaller arteries are also often the seats of syphilitic changes, which tend to occlusion but not to aneurysm. Such lesions in the vasa vasorum of the aorta lead to changes in the middle coat of a gummatous nature, which tend to go on to scar-tissue formation, the yielding of which results in the development of aneurysm.

Backhaus, Chiari, and others have supported these conclusions by pathological observations, and Straub found mesaortitis in 69 out of 84 cases of general paralysis, and in only 7 out of 71 other assorted diseases, though all the seven subjects had had syphilis.

Chiari found that the mesaortitis developed between the ages of 30 and 60, half of his cases being between 31 and 40 years of age. Backhaus obtained a history of syphilis in 5 out of 7 cases of mesaortitis.

Dr. Mott is of the opinion that syphilitic arteritis affecting the coronary arteries may give rise to severe symptoms of cardiac degeneration. The heart undergoes fatty degeneration from insufficient nutrition. In two cases there were symptoms of cardiac dilatation: the pulse was hardly to be felt at the wrist, though when one hand was placed over the cardiac area the impulse was forcible, and diffused over a considerable surface; the other hand upon the pulse detected the fact that many of the beats were not forcible enough to produce a pulse-wave in the radial artery. Such cases are generally rapidly fatal; the patients first complain of breathlessness on exertion without obvious cause, of fainting feelings from cerebral anaemia, especially on assuming the erect posture, of giddiness and vertigo. These cases are of extreme importance from the point of view of life insurance, as men between 20 and 40, who have had syphilis, but who have no signs of valvular disease, may yet exhibit symptoms of cardiac degeneration most difficult to account for. Often there is arrhythmia, and the pulse may sometimes be slow, sometimes quick. Anginal spasms frequently occur.

Sir William Gowers thinks that arterial disease may be taken

as the most conspicuous danger in the early years after syphilitic infection. 'Every case of sudden hemiplegia, sudden and therefore of vascular origin, occurring between the ages of 18 and 48, without Bright's disease, without heart disease, in an individual who is known to have had syphilis, may be confidently ascribed to syphilitic arterial disease.' Of 40 such cases in his experience, about one-quarter occurred in the first two years after acquiring syphilis, about half occurred in the first five years, nearly three-quarters in the first seven years, four-fifths in the first ten years, and the others scattered over the next seven years.

Runeberg is strongly of the opinion that syphilis, apart from its effects upon the arteries of the brain, affects seriously the circulatory organs to a much greater extent than is generally recognized. The lesions may be of varied nature, but the most important are gummatous affections of the arteries and of the heart muscle, such as aortitis, with consequent dilatation or aneurysmal formation, with valvular affection in some instances, coronary arteritis with myomalacia and connective-tissue formation in the heart muscle, as well as diffuse gummatous myocarditis. In his opinion, the mortality from heart and aorta syphilis is not much less than that for brain and spinal cord lesions. He believes that in due time it will be more generally accepted that syphilis of the circulatory apparatus is recognizable during life, and submits the following as the most important symptoms of such a condition: paroxysmal attacks of anginal pain or cardiac asthma, unequal and irregular heart-contractions with dull sounds, indistinct pulse-wave and occasionally cardiac murmurs if the aortic orifice be involved in the pathological process, and finally, in some cases, signs of heart-failure with hypertrophy and dilatation. When these symptoms occur in young and middle-aged persons without general arterial sclerosis, or without any other definite cause being present, and especially when there is a history or other indications of syphilitic infection ten years or so previously, the diagnosis of cardiac syphilis is scarcely to be doubted.

In Blaschko's opinion, sequelae of syphilis in the circulatory system are :—

1. Apoplexy, with endarteritis basis.

2. Syphilitic heart-affections are a frequent form of late syphilis. They can occur as diffuse myocarditis; circumscribed heart gummata; endocarditis with resulting genuine valvular defect, especially aortic insufficiency; and syphilitic sclerosis of the coronary arteries.

3. Aortic aneurysm is one of the most frequent and most serious local results of late syphilis. This affection, apart perhaps from a few cases in older people, with distinct general arteriosclerosis, and a few cases resulting from injury, is, according to the accurate researches of Döhle, Heller, Chiari, Benda, &c., almost universally recognized as being a syphilitic affection.

Aneurysm. The evidence in favour of aneurysm being very commonly the result of previous syphilitic infection is very considerable. Apart from the observations on the mesaortitis which causes aneurysm, there is a large amount of clinical and other pathological material which supports this view. Dr. Mott recalls very few cases of aneurysm of the aorta in men from whom he had not been able to obtain or detect a specific history.

Welch, in 1876, found in 34 cases of aneurysm in soldiers that 17 were undoubtedly syphilitic and 8 were probably so. He found further, in necropsies on 56, the subjects of syphilis, that 60 per cent. had disease of the aorta.

It is probable that toxic influences, such as chronic alcoholism and plumbism, and also those blood dyscrasias which raise arterial pressure, will tend to internal strain of these vessels, and render them more liable to disease, especially the aorta and coronary arteries. In the case of the aorta and coronary arteries, physical exertion plays a most important part in the symptoms and complications that may arise in connexion with syphilitic disease—such as sudden rupture of the aorta, formation of false dissecting and true aneurysms.

Nearly all authors agree that syphilitic arteritis is much more likely to occur in persons who have not been specifically treated.

Prof. Osler writes: 'It is notorious that a history of infection, even in persons with well-marked signs of the disease, is not easy to get, particularly in women. There are a great many cases

in which syphilis is latent, but the more clearly the question is looked into the more one becomes impressed with the importance of syphilis as the essential factor in the causation of aneurysm in persons under 45 years of age.'

The following are the views of some observers on the frequency of syphilis as a cause of aneurysm:—

Welch . . .	66	per cent. have had syphilis
Malmsten . .	80	„ „ „
Hampeln . .	82	„ „ „
Heller . . .	85	„ „ „
Etienne . . .	69·7	„ „ „
Pansini . . .	65	„ „ or including doubtful cases, 84 per cent.

Von Hanseemann could only find in 18·75 per cent. of 54 cases of aneurysm a history or evidence of syphilis, and he does not regard all cases of aneurysm, even in syphilitic subjects, as due to specific infection. He also states that he could only find 3·43 per cent. of 350 syphilitics to be suffering from aneurysm ; but in commenting on this, Heller, who was one of the first observers to support the theory of the frequent syphilitic origin of aneurysm, showed that in 400 cases of syphilitic post mortems he found 3 per cent. aneurysms, 2 per cent. brain syphilis, and 2 per cent. heart syphilis. On the other hand, in 745 post-mortem examinations on adult tuberculous cases, aneurysm occurred in only 0·13 per cent.

Dr. Newton Pitt looks upon syphilis as by far the most frequent and important cause of a thoracic aneurysm, but it is overstating the case to say, 'No syphilis, no thoracic aneurysm.'

An aneurysm due to syphilis generally develops within twelve years of infection. The maximum of aneurysms is between the ages of 30 and 40.

Von Düring reports that syphilis and aneurysm are unusually common amongst the Turks, who, however, drink no alcohol.

The following are, according to Prof. Osler, among the important features of syphilitic aneurysm. It occurs, as a rule, in persons under 40 ; the ascending arch is most apt to be involved ; angina pectoris may be an early symptom ; aortic insufficiency is often associated with it ; the aneurysms are frequently multiple—five, seven, and nine have been described ; other features may be present, e. g. gummata of the liver or bones, or locomotor ataxia.

He further states that attacks of severe angina pectoris may occur in the early stages of aortic aneurysm, and that the cases are met with in comparatively young men who have had syphilis.

In Krehl's opinion, syphilis may attack any portion of the heart. In the pericardium the disease produces fibrous inflammation and gummata; the blood-vessels may be attacked by syphilitic endarteritis, and all the effects of coronary sclerosis may make their appearance. The lesions of the muscle are, first, the effects of the vascular disease; secondly, diffuse interstitial inflammation or true myocarditis; and thirdly, gummata, which vary greatly in number, size, and location. Add to these changes cicatricial, verrucous, and gummatus processes in the endocardium.

Dr. Babcock is of the opinion that angina pectoris, when occurring in a person under 45, is very suspicious of coronary sclerosis due to syphilis.

In the cases of aneurysm of the aorta which I investigated in the Manchester records, a history of venereal disease was only given in 27 per cent. of the cases in which notes were obtained, syphilis being acknowledged in 16 per cent. and gonorrhoea in 11 per cent. Evidence of previous syphilis was obtained from 160 post-mortem examinations, in 15 cases undoubtedly (9.3 per cent.), in 14 other cases probably (8.7 per cent.); that is, possibly in 29 cases altogether (18 per cent.).

In the Manchester autopsies on 87 subjects showing syphilitic lesions the circulatory system was affected 29 times, 17 of these being aneurysm or dilatation of the aorta, and 11 disease of the cerebral vessels.

In view of the foregoing evidence it can hardly be doubted that syphilis plays an important part in bringing about serious and fatal diseases of the circulatory system, and at a comparatively early age.

SYPHILIS OF THE LIVER

Traces of previous syphilitic infection are not uncommonly found in the liver at post-mortem examinations. The most frequent appearances are scars of old gummata, gummata them-

selves, and more general hepatitis or fibrosis. Clinically, the condition is not very commonly diagnosed, and death from syphilitic disease of the liver is still less frequently met with. But whilst this is the case, there are some observers who consider that it is probable that the ordinary alcoholic cirrhosis occurs in subjects who have had syphilis at one time of their lives, and that alcoholic excess alone will not cause the ordinary so-called alcoholic cirrhosis. Some look upon this latter condition as a parasymphilide of the liver.

Albert Ramsbottom's observations on alcoholic cirrhosis do not support this view, for he was unable to obtain a history of syphilis in any one of the fifty-nine cases which he reported, nor were there any signs of previous syphilis found in the post-mortem examinations.

In the 87 Manchester cases showing evidence of syphilis at the autopsy the liver was affected 51 times. In 36 of these cases there were only scars indicating the seats of previous gummata.

For further information on visceral syphilis the section of this System by Professor Osler and Dr. Gibson should be referred to (vol. iii, pp. 1-80).

SYPHILIS OF THE KIDNEY

Nephritis is not uncommonly associated with syphilis both in the secondary and tertiary stages. Such cases are recognized more often on the Continent than in England. Syphilitic albuminuria is especially prone to develop during the first year after infection. At this period the most characteristic feature of the nephritis is the large amount of albumen present in the urine, and in many cases there are no other signs of renal disease than the albuminuria. Some of these cases often improve remarkably under treatment with mercury (Dr. Rose Bradford). In the 87 Manchester syphilitic autopsies scars indicating previous gummata were found in the kidneys 11 times. Gummata occurred once and possibly twice, and amyloid changes twice. Granular nephritis was present in 8 cases, parenchymatous nephritis in 5, and mixed nephritis in 1 case. Surgical kidney was found in 3 cases.

SYPHILIS AND TUBERCULOSIS

Sergent, one of the chief supporters of the view that syphilis frequently predisposes to the onset of phthisis, in 'Syphilis et Tuberculose' brings forward a considerable body of clinical evidence to show that syphilis plays an important part in the causation of tuberculosis by preparing a very favourable soil for the growth of the infective agent of the latter disease in its many clinical manifestations. In his opinion pulmonary tuberculosis is much more frequently of syphilitic origin than is generally held to be the case, and he describes it as occurring both in early and late stages of syphilitic infection. It may develop in the second or third year after syphilitic inoculation in cases in which inadequate treatment has been carried out, and in which the system is considerably lowered in its vitality and in a most favourable condition for the growth of the tubercle bacillus, which may proliferate rapidly, causing acute and rapidly fatal phthisis. To the period of later tuberculization belong many cases of fibroid phthisis or pulmonary sclerosis. Sergent maintains that in these cases, and also frequently in others diagnosed as chronic bronchitis or emphysema, he can find evidence of syphilitic infection in the form of inequality of the pupils, sluggish or absent reaction of the pupil to light stimulus, or especially in the form of buccal leukoplakia. He refers to the observations of other French observers who support these views, and quotes Landouzy as saying 'La syphilis fait le lit de la tuberculose'.

Fournier says: 'I have already seen a number of young subjects in whom syphilis had powerfully exerted its depressing influence become tuberculous in the first months or the first years of infection. I even venture to state that, under these conditions, phthisis sometimes pursues a rapid course and is soon fatal. Again, from my own personal experience, as well as from what has been said on this subject by the highest authorities, I do not hesitate to inscribe syphilis in the etiological chapter of pulmonary tuberculosis.'

In Dr. C. F. Marshall's opinion, when tuberculosis develops in a subject with recent syphilis it pursues a rapid course, and is usually fatal, especially when the subject is also alcoholic. On the other hand, tuberculosis attacking an old syphilitic is generally slow and benign in evolution, and the general health may remain good for a considerable time, in spite of signs of cavitation and abundant bacilli.

Dr. Douty, during five years' observation of patients in high alpine latitudes, came to the conclusion that 30 per cent. of the men with phthisis were syphilitics, perhaps more. They were of the upper middle classes, as a rule, and had lived hard-working business lives and were between 30 and 40 years of age. The nationality of these men is not stated. He adds that many directors of sanatoria and hospitals on the Continent tell him that the proportion of syphilitics amongst phthisical men is 30 to 40 or even 50 per cent. Klause had told him that in the phthisical wards at the Charité, Berlin, 50 per cent. of the men were syphilitic.

Dr. F. W. Andrewes, in the first volume of this System, writing on the general pathology of syphilis, says: 'It must be mentioned that tubercle is no uncommon complication of late syphilis. Many syphilitics die of pulmonary tuberculosis; much of what was at one time regarded as syphilis of the lung was probably in truth tubercle.'

Sir Jonathan Hutchinson has seen 'a great number of syphilitic patients suffering from phthisis. It is extremely frequent for syphilis to pass into phthisis.' But he does not express any opinion as to the syphilitic infection having predisposed the patient to the development of the phthisis. He is of the opinion that in connexion with syphilitic scars conditions which are characteristic of tuberculosis may be produced, and that syphilitic forms of inflammation may be associated with recent tuberculosis.

The broad view of the subject which he takes is that a tendency to tuberculosis may be modified by the introduction of syphilitic poison, not that the latter poison may predispose to or encourage the development of the tuberculosis.

Mr. D'Arcy Power, too, draws attention (vol. ii, p. 12) to the frequent interaction of syphilis and tubercle in the bones and joints of patients at all ages and in every condition of life.

The percentage of deaths from phthisis among 160 syphilitics examined by Mathes was only 27, which is not much greater than that for deaths of non-syphilitics.

On the other hand, there are observers who do not consider that syphilis plays much part in the etiology of pulmonary tuberculosis.

Sir Dyce Duckworth believes that no part of the body escapes syphilitic lesions so frequently as the lung, and that it is very rare to be able to point to a morbid lesion there and say that it is of syphilitic origin. Whether or not the condition of syphilis, which is a blight to the whole nutrition of the body, may not predispose a person to become the subject of tuberculosis more than one who is not syphilitic, is a question for further consideration.

Dr. Samuel West's view is that 'there is certainly no liability to phthisis among syphilitic persons, and indeed, considering the frequency of the two diseases, the rare association of the two together is striking, and suggests an antagonism rather than a relationship between them'.

Dr. Percy Kidd writes that 'a history of syphilis is not rarely obtained from phthisical patients; but if the former disease be possessed of any etiological influence it can only be of an indirect character'.

Dr. Walters estimated that syphilis was an accessory cause of tuberculosis in about 5 per cent. of 134 male patients.

Tuberculosis of the respiratory organs occurred twelve times in 62 male and five times in 25 female subjects showing post-mortem evidence of previous syphilitic infection, in the records of the Manchester Royal Infirmary. In the males, syphilitic laryngitis occurred twice, healed phthisis three times, syphilomata of the lungs once, and pulmonary tuberculosis six times. In the female cases, healed phthisis, fibroid phthisis, acute and ordinary pulmonary tuberculosis each occurred once. The average

age at death of these tuberculous cases was 45 years, excluding one, a boy aged 11 who died of syphilitic laryngitis. Death was probably due to the tuberculous lesions in nine of these cases.

SYPHILIS AND CANCER OF THE MOUTH

Syphilis and Leukoplakia

In Mr. D'Arcy Power's opinion (vol. ii, p. 87), leukoplakia bears a very intimate relationship to syphilis, and although it is not yet possible to state that every case of leukoplakia is syphilitic, it is remarkable how few other causes of chronic irritation produce this particular change in the mucous membranes. Milian, in his official report upon leukoplakia made at the International Congress of Medicine held at Lisbon in 1906, arrived at the conclusion that idiopathic leukoplakia starts from syphilis. But probably, whilst syphilis undoubtedly has a considerable effect in the causation of the disease, there are other factors besides, the chief of which are alcohol and tobacco irritation.

Mr. W. G. Spencer writes : ' Tobacco, carious teeth, irritating tooth-plates, are the common local causes of leukokeratosis, and are sufficient to produce the affection ; but syphilis, alcohol, &c., contribute to produce the patches.

' Acquired syphilis is the chief general cause of leukokeratosis, although this has followed the congenital form. So important is syphilis in this respect, that leukokeratosis in a man who has not smoked, and in a woman, suggests unrecognized luetic infection, possibly of extra-genital origin.

' A well-marked leukokeratosis may become epitheliomatous at any time.'

Trapenard, in a thesis on the subject (Paris, 1905), stated that he found leukoplakia to be always of syphilitic origin and due to an embryonic connective-tissue formation caused by endoperiarteritis and differing from other syphilitic lesions by the presence of epidermic globes, which predispose it to become epitheliomatous under the influence of some irritant. He found

evidence of syphilis in 92 per cent. of the cases he collected, and considered that *syphilis ignota*, or hereditary syphilis, would account for the rest.

Syphilis and Cancer of the Tongue.

Mr. H. T. Butlin, writing on the causation of cancer of the tongue, says :—

Of syphilis it may, we think, be said that in so far as it is capable of producing ulcers and scars of the tongue. so far is it capable of predisposing the tongue to the occurrence of carcinoma. But the ulcers and scars produced by syphilis are not more prone to become cancerous than the ulcers and scars which are due to any other cause. Nor is the psoriasis (leukoma) or chronic superficial inflammation produced by syphilis more apt to become cancerous than psoriasis or chronic superficial glossitis which has no connexion with syphilis. But the influence of syphilis is not limited to the power it possesses of producing superficial inflammation of the tongue. It is prone to leave scars along the borders of the tongue, and these, when they are irritated, may at a later period become cancerous ulcers. Even the fissures and scars left by the breaking of deep-seated gummata may afterwards become the seat of carcinoma. Such cases are probably very rare.

Fournier finds that buccal leukoplakia is the rule amongst syphilitic smokers, and among 184 cases of cancer of the mouth seen in his private practice, 155 had decided syphilitic antecedents, i. e. 84 per cent. In the 29 other cases the antecedents were not given.

This form of cancer is especially common in males (176 out of 180 cases). It is especially a disease of middle or advanced life, the maximum number of cases (12) at any one age being in Professor Fournier's experience at 52 years. The following table shows the ages in 133 of his cases :—

From 35 years (lowest) to 39 years	9 cases
„ 40 „ „ 49 „	38 „
„ 50 „ „ 59 „	52 „
„ 60 „ „ 69 „	25 „
Over 70 „	9 „

As a necessary corollary, it is found that this cancer is a manifestation of old syphilis. It attains its maximum frequency

from the twentieth to twenty-fifth year after infection, as the following table shows :—

From 7th to 10th year of infection	6 cases
„ 11th „ 20th „ „	31 „
„ 21st „ 30th „ „	45 „
„ 31st „ 40th „ „	28 „
„ 41st „ 50th „ „	10 „
„ 51st „ 56th „ „	3 „

Although syphilis produces cancer of the tongue, it only does so exceptionally by itself. It has need of a collaborator, which is tobacco, which helps cancer to develop in these cases, because it is rare (*a*) in syphilitics who do not smoke, and (*b*) it is very rare in women, who do not smoke or who use tobacco in moderation compared to men. Syphilis has a predominating harmful influence, for in some cases it alone is sufficient, but few syphilitics who do not smoke ever develop cancer ; still fewer cases are found in smokers who are non-syphilitic, although many smoke to great excess.

Syphilis rarely leads in a direct way to cancer. The rule is that it only does so by the intermediary of a specific lesion, i. e. leukoplakia.

Poirier believes that everybody cannot have cancer of the tongue—you must be a smoker or syphilitic, or better still, a syphilitic and a smoker ; and those who combine those two conditions, especially the latter, have a much greater risk than other people. So true is this, that cancer of the tongue might be called the cancer of syphilitic smokers. Of the 32 cases operated on by him in the last five years, 27 were syphilitic, and in 3 of the remaining cases a stricter inquiry might have revealed syphilitic antecedents.

Etcheverry records a number of cases in which cancer of the tongue developed in people who had previously had syphilitic affections of the tongue, and concludes that syphilis exercises an active influence on the development of cancer of the tongue, and that this influence may be exercised in three ways :—

(*a*) Cancer follows syphilis through an intermediary stage of leukoplakia.

(*b*) Cancer develops on local lesions, such as chronic mucous plaques, cicatrices of gummata, &c.

(c) And perhaps syphilis acts as a general cachexia-producing agent.

He quotes other writers in support of his views.

These opinions show that there is a decided danger of cancer of the tongue supervening on buccal leukoplakia, which is predisposed to by syphilitic infection. I have not been able to find any figures showing the frequency of the occurrence of cancer of the mouth in syphilitics or amongst the assured, nor could I find any observations suggesting that cancer of other organs is attributable in any special degree to syphilis.

EFFECT OF TREATMENT ON AFTER-RESULTS OF SYPHILITIC INFECTION

Dr. Mott states that, if on the one hand we take 100 people infected with syphilis, and treat them with mercury in a thorough manner, experience shows that a smaller percentage will develop syphilitic disease of the nervous system or the so-called parasymphilitic affections; but yet a certain number, in spite of thorough treatment, develop one or the other; moreover, it does not seem to prolong the average interval between the infection and the development of the disease. If, on the other hand, we take 100 people infected with syphilis who have either not been treated at all or but imperfectly, only a certain percentage will suffer seriously. Experience shows that the number of syphilitic, and particularly late parasymphilitic, affections of the nervous system will be greater than in those treated. Statistics of various authorities differ in percentages as regards this question. Unfortunately, the comparison is not quite fair, because the people who are not treated are generally those who have a mild attenuated form of the disease in which the primary sore and secondary symptoms are not well defined.

Syphilis and General Paralysis. Fournier believes that general paralysis is due to two great causes—syphilis and insufficient treatment.

He states that 78 per cent. of cases of tertiary syphilis give

a history of insufficient or improper treatment. His observations on 2,396 cases of tertiary syphilis were :—

No treatment at all	197
Mercurial treatment for less than 3 months	490
" " " " 6 " 	399
" " " " 12 " 	594
" " " " one year	146
" " " " 1 to 2 years	357
" " " " 2 to 3 years	98
" " " " 3 years	34
" " " " more than 3 years	29
Iodide treatment only	45
Treatment by sarsaparilla, &c.	7
	<hr/>
	2,396

Fournier also states that 90 per cent. of tertiary lesions follow secondary syphilis of a more or less benign character, probably because patients with mild secondary symptoms are less likely to persevere with treatment than those suffering from severe symptoms. Mr. Buxton Shillitoe found that only about 1 per cent. of those patients in whom he had treated the primary lesion developed tertiary lesions.

It is generally recognized that thorough treatment by mercury, if adopted in the early stages of infection, will, in the majority of cases, ward off the development of sequelae, but there are different views as to what constitutes such thorough treatment, which are given in other sections of this System. But whilst thorough treatment will probably ward off later manifestations of disease, it would not do to accept for assurance an applicant in the early stages of infection on condition that he submitted himself to proper treatment, there being no guarantee that he would carry out his undertaking properly.

Other views as to the effects of treatment in warding off the possibilities of the sequelae of syphilitic infection are referred to in the opinions of the various medical referees on the eligibility of syphilitics for assurance.

CHAPTER XVII

EXPERIENCES OF ASSURANCE COMPANIES IN THE MORTALITY OF SYPHILITICS

THE returns of insurance companies' experiences of the mortality of syphilitics are very valuable for actuarial purposes, but they are not altogether satisfactory, for although an applicant for a policy is asked, directly or indirectly, the question of previous syphilitic infection, only a minority of those who really have suffered from the disease say so; either from the deliberate intention of suppressing a fact in their medical history which they would rather forget, or from real forgetfulness, or indeed at times from ignorance, for mild doses of the poison may pass without the real ailment being recognized. Some companies also only ask for medical history within a certain number of recent years, which may easily exclude the time of a syphilitic inoculation.

Runeberg, in 1900, published an important contribution on the value of syphilitics for assurance purposes. He examined the causes of death of 734 policy-holders in the Finnish Kaleva Life Office.

Of these 734 cases, 78 acknowledged, in their proposal, having had syphilis, and 656 did not. Of the former group 20 died from other than syphilitic sequelae. The deaths from sequelae of syphilis were 58 amongst the acknowledged syphilitics, and 26 from the 656 unacknowledged, making a total of 84 or 11·4 per cent. of all the deaths. There were therefore, according to Runeberg's findings, 11·4 per cent. of the total number of deaths certainly due to syphilitic causes, and 15 per cent. with more or less probability due to the same.

Runeberg thought that he had underestimated the number of cases in which death was more or less consequent on previous syphilitic infection, and gives a table of 47 cases in which there was no history of syphilis, but in which death occurred under the age of 50 from 'heart-stroke', cerebral haemorrhage, or

cerebral softening. He thinks that 75 per cent. of these cases of apoplexy, and about 50 per cent. of the heart-stroke cases, are probably due to syphilitic causes, and if this be so, the deaths brought about more or less by syphilitic infection amount to 131 or 15 per cent.

This 15 per cent. mortality from supposed syphilitic causes compares with 21 per cent. from tuberculous lesions and 10 per cent. from pneumonia.

The causes of death which Runeberg attributed to syphilis in the 84 policy-holders were as follows :—

Various heart affections	31
Brain and spinal cord diseases	21
Progressive paralysis	22
Chronic nephritis	3
Aneurysm and atheroma of coronary arteries	2
Arteriosclerosis	2
Caries	1
Unilateral pulmonary cirrhosis	1
Tumour of the neck	1
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	84
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The causes of death in the other 47 cases were mostly syncope, apoplexy, or cerebral softening, which Runeberg attributed to syphilis in 50 per cent. of the cases of heart-stroke and 75 per cent. of brain lesions.

Runeberg shows the increased mortality of syphilitics by the following calculation. Of 11,359 proposals, 10,740 with 656 deaths were without a history of syphilis (= 6.1 per cent.).

Of 619 proposals in which syphilis was acknowledged, there were 78 deaths (= 12.6 per cent.), which is twice the other mortality.

The ages of death of the 84 certain syphilitic cases were :—

21-30 years	5 cases
31-40 „	33 „
41-50 „	29 „
51-60 „	16 „
61-70 „	1 case

with an average age of 43.4 years.

The length of the applicants' lives after infection with syphilis was :—

<i>Years after Infection.</i>	<i>Cases.</i>
1-5	1
6-10	8
11-15	16
16-20	16
21-25	9
26-30	10
31-35	6
36-40	3

Or, on an average, death occurred 20·2 years after infection.
Death followed the issue of the policies—

<i>Years.</i>	<i>Cases.</i>
1	1
5	32
10	27
15	14
20	10

That is, an average of 8·1 years after becoming assured.

Runeberg's findings are very hard to accept. Thus, if we take 20 per cent. of the 656 cases which did not declare syphilitic infection and add these to the 78 who did, we have 209 cases of syphilitic infection in the whole 734 considered. In these 209 cases were 84 deaths attributed to sequelae of syphilis, that is, over 40 per cent.

Tiselius, an actuary (1904), examined the proposal forms in Scandinavian assurance companies of 5,175 people who had acquired syphilis before assuring, and his conclusions support those which Runeberg drew from his investigations. Of these, 850 had died, whilst only 660 deaths had been expected. Of these 850 deaths, 150 (= 17·65 per cent.) died from diseases definitely attributable to syphilis; 254 (= 29·88 per cent.) from diseases possibly or probably attributable to syphilis; and 446 (= 52·47 per cent.) from causes which had no direct relation to syphilis.

The 850 deaths of those who had syphilis at the time of assuring are divided into three groups :—

A. Directly due to syphilis :

1. Diseases of the heart and blood-vessels	31
Aneurysms	29
2. Diseases of the central nervous system	109
General paralysis	87
Tabes	9
3. Diseases of the liver	2
4. Syphilis	8
	<hr/>
	150
	<hr/>

17·64 per cent. of the 850 cases.

B. Probably due to syphilis :

1. Diseases of the heart and blood-vessels	122
Arteriosclerosis	39
Paralysis of the heart	37
2. Diseases of the central nervous system	125
Apoplexy	87
3. Insanity	4
4. Amyloid degeneration	2
5. Obstruction to air-passages	1
	<hr/>
	254

29.88 per cent. of the 850 cases.

C. Other causes :

1. Diseases of the heart	23
2. Diseases of the central nervous system	10
3. Diseases of the genito-urinary system	63
4. Diseases of the liver	16
Cirrhosis	13
5. Diseases of the intestines (not cancer)	12
6. Diseases of the blood	6
7. Diabetes	7
8. Diseases, infectious (not cancer)	111
Pneumonia	54
9. Tuberculosis	78
Pulmonary	68
10. Tumours	42
Cancer	34
11. Chronic poisoning	6
Alcohol	4
12. Emphysema	2
13. General exhaustion	1
14. Violent death	67
Suicide	45
15. Cause unknown	7
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	451

52.47 per cent. of the 850 cases.

[Though copied correctly, there are 5 too many cases in the C table. Probably 78 tuberculosis cases ought to read 73, making the total 446 and not 451, and grand total of all the tables 850.]

Tiseliuſ adopts very cloſely the leſions attributed by Runeberg to the effects of ſyphilis. He compared the actual mortality with the expected mortality of theſe caſes. The numbers of lives conſidered were as follows :—

	<i>Number.</i>	<i>Deaths.</i>	<i>Percentage.</i>
Normal rates . . .	2,511	440	17.5
Increased premium .	2,864	423	14.8
The whole material .	5,175	850	16.4

MORTALITY OF SYPHILITICS

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TABLE OF EXPECTED AND ACTUAL MORTALITY FOR AGE GROUPS OF POLICY-HOLDERS WITH HISTORY OF SYPHILIS.

A. ACCEPTED AT NORMAL RATES.

<i>Ages.</i>	<i>Expected mortality. Seventeen English Companies' table.</i>	<i>Actual mortality.</i>	<i>Actual mortality in percentage of expected mortality.</i>
20-30	12	14	116.7
30-40	79	76	96.2
40-50	119	160	134.5
50-60	96	124	129.2
60-70	40	53	132.5
70-80	11	11	100.0
20-80	357	438	122.7

B. INCREASED PREMIUM.

<i>Ages.</i>	<i>Expected mortality. Seventeen English Companies' table.</i>	<i>Actual mortality.</i>	<i>Actual mortality in percentage of expected mortality.</i>
20-30	25	23	92.0
30-40	105	118	112.4
40-50	98	145	148.0
50-60	59	93	157.6
60-70	29	38	131.0
70-80	5	6	120.0
20-80	321	423	131.8

C. THE WHOLE MATERIAL.

<i>Ages.</i>	<i>Expected mortality. Seventeen English Companies' table.</i>	<i>Actual mortality.</i>	<i>Actual mortality in percentage of expected mortality.</i>
20-30	36	37	102.8
30-40	180	192	106.7
40-50	210	301	143.3
50-60	150	212	141.3
60-70	68	90	132.4
70-80	16	16	100.0
20-80	660	848	128.5

[The figures do not tally with the total numbers of lives considered in the first table, but they are copied accurately from Tiselius's original paper.]

MORTALITY AMONGST THE ABOVE PROPOSERS ACCEPTED AT INCREASED PREMIUMS OR REJECTED, IN PERCENTAGE RELATION TO THAT OF THE SEVENTEEN ENGLISH COMPANIES.

<i>Ages.</i>	<i>Increased premium.</i>	<i>Rejected.</i>
20-30	96.6 per cent.	144.5 per cent.
30-40	89.4 "	155.6 "
40-50	107.3 "	155.4 "
50-60	120.0 "	150.6 "
60-70	112.1 "	123.1 "
70-80	102.0 "	102.9 "

Tiselius therefore came to the following conclusions: The mortality curve for syphilis lies between that for persons who are taken at an increased premium and that for those rejected, and each assurance of a syphilitic at ordinary rates must always be held to be objectionable. The mortality of syphilitic proposers who were taken at a normal premium was much higher than amongst all other proposers taken at an increased premium, and the mortality of those syphilitic proposers who were accepted at an increased premium still much greater than amongst those who, for other causes, were taken at increased rates. For ages over 50 the mortality amongst high-premium syphilitic policy-holders was greater than amongst those rejected altogether. He recommends, therefore, an increased premium of from 20 to 50 per cent. for each proposer with a history of syphilis.

Salomonsen, much impressed by Runeberg's views on the risks of syphilitic proposers, and still more by Tiselius's support of Runeberg, examined the records of his own company, 'Danmark.' He found that 121 persons had acknowledged in their proposal forms having had syphilis. Of these, 17 were dead, 5 from causes attributable to syphilis and 12 from other causes, and yet the mortality expectations were only 9.14. The average age for all deaths was 46 years.

This investigation, limited though it was, supported the larger statistics of Tiselius, and showed that syphilitics have a heavy extra mortality at comparatively early ages, and that insurance companies have suffered much loss by them.

In Salomonsen's opinion, Tiselius ignored the date of infection and the method of treatment of the syphilitic policy-holders, and thereby lessened the value of his statistics, for the estimate of a syphilitic life must be greatly affected by the fact of good, or poor, or no treatment. He urges that the first years after infection involve little or no danger to life, but on the contrary the danger of death from tabes, general paralysis, and other tertiary symptoms occurs much later—thirteen, fifteen, or even twenty years after infection. It seems therefore rational, however paradoxical it may appear at first sight, in the case of syphilitics who have carried out Fournier's treatment thoroughly,

to insure them soon after the disappearance of the secondary symptoms (usually about two years from infection), but only on an endowment policy maturing between 40 and 50 years of age and with a premium slightly (though not so much as heretofore) increased.

Blaschko and Jacobsohn examined the causes of 5,724 deaths in the Victoria (Continental) Insurance Company.

Among the 150 insured who either gave a history of syphilis or who, from their statements, had most probably been infected—

10	died from	tabes	=	6.6	per cent.	of deaths.
36	"	"	progressive	paralysis	.	.	=	24.0	"	"
4	"	"	aneurysm of the	aorta	.	.	=	2.6	"	"

that is, 50 (= 33 per cent.) cases certainly were syphilitic.

Moreover, there were—

8	deaths from	apoplexy	under 50 years of age.
1	"	"	bulbar paralysis.
6	"	"	cirrhosis and other affections of the liver.
7	"	"	nephritis: granular kidney.
2	"	"	cerebral tumour.
2	"	"	syncope and cardiac disease in young people.
1	"	"	myocarditis.

In all, 27 more or less probably attributable to syphilis.

There were therefore, of the 150 policies, 50 in which syphilis was the cause of death, that is, 33 per cent.; and 27 more, that is, 52 per cent., in which it was most probably the cause of death.

They found a large number of cases of tabes, general paralysis, and aneurysm of the aorta on the certificates of death in their company in 5,574 policy-holders who did not give a history of syphilis. They had no doubt that deaths from these three diseases were due to syphilis; and there was also one death certified as due to syphilis and many as due to diseases of the blood-vessels and viscera, which were more or less probably caused by syphilis.

The deaths from the three special diseases were :—

Tabes	.	.	.	44	=	0.7	per cent.	of non-syphilitic history cases.
Progressive paralysis	.	.	.	218	=	3.9	"	"
Aneurysm of the aorta	.	.	.	33	=	0.6	"	"

In all 295 deaths due to syphilis.

In addition, 127 of 469 cases of various heart, liver, kidney, and brain affections could with great probability be put down to syphilis. If it be assumed that of the 5,574 deaths 20 per cent., i.e. 1,115, of the assured had syphilis, then 26.5 per cent. of these certainly and 40 per cent. probably died from syphilitic sequelae. Taking the average between these percentages, Blaschko concludes that, in round numbers, one-third (33 per cent.) of all policy-holders who have had syphilis at one time, and 6 per cent. of *all* policy-holders, die sooner or later from syphilitic sequelae.

These percentages are very high, and the writers probably included too many diseases as sequelae of syphilis.

	<i>Total No. of deaths from all causes.</i>	<i>Due to syphilis.</i>	<i>Probably due to syphilis.</i>
Runeberg	734	58 = 11.4 per cent.	131 = 15.0 per cent.
Blaschko	5,574	295 = 5.2 „	127 = 7.7 „

Kleinschmidt, to form an idea of the share taken by syphilis in the causes of death among insured lives, undertook an examination of all the cases which had entered the 'Vaterland' Life Assurance Association during a considerable space of time. The inquiry was not limited to the deaths of those persons who, at the time of insurance, stated that they had had syphilis: for the statements of applicants on the subject of past venereal complaints are, for various reasons, not implicitly to be relied on.

The basis of his investigations is the whole of the deaths occurring from 1872 to the end of 1904, 2,503 in number. The influence of syphilis is principally manifested in the so-called metasyphilitic diseases. As such he regards the majority of cases of general paralysis of the insane, and of tabes dorsalis, the endarteritis of the brain-arteries described by Hubner, mes-aortitis and the aortic aneurysms which arise therefrom, and the symptoms which result from disease of the coronary arteries and of the myocardium, with, in addition, a portion of the affections of the cardiac vessels, focal degenerations of the heart muscle, premature calcification of arteries, with or without con-

tracted kidney, a certain form of cirrhosis of the liver, and some other conditions.

Among the causes of death of 88 persons who owned to syphilitic infection, he found—

	<i>Of 88 syphilitics.</i>	<i>Blaschko's percents.</i>	<i>Of 2,415 other deaths.</i>	<i>Blaschko's percents.</i>
General paralysis of the insane .	16 = 18.1 per cent.	24.0	70 = 2.9 per cent.	3.9
Tabes dorsalis .	4 = 4.5 „	6.6	14 = 0.58 „	0.7
Apoplexy (age under 50) .	5 = 5.6 „	—	53 = 2.2 „	—
Brain and spinal cord lesions, not accurately diagnosed (age under 50) .	3 = 3.4 „	—	14 = 0.56 „	—
Aortic aneurysm	2 = 2.27 „	2.6	10 = 0.41 „	0.6
Heart-failure, myocarditis, &c. (age under 50)	8 = 9.0 „	—	21 = 0.87 „	—

From this statement of the figures a connexion between the said diseases and syphilis is established. The deaths of persons who gave a history of syphilis at the time of admission could be traced back to that disease as a cause in no less than 51 per cent. of the cases. The other cases of death where syphilis was suspected could be brought in greater or smaller degree into etiological relation with syphilis. By careful calculation Kleinschmidt came to the conclusion that 155 deaths were the result of syphilis, or 6.2 per cent. of the whole deaths.

In deducing his conclusions, Kleinschmidt assumed that syphilis was the predisposing cause of death in 90 per cent. of his cases of general paralysis and tabes, in 75 per cent. of his cases of aneurysm of the aorta, and in 25 per cent. of his cases of apoplexy, syncope, &c., and brain and spinal cord disease under 50 years of age.

Ages at death of 88 syphilitic policy-holders (Kleinschmidt) :—

Age 21-30 years	2 cases.
„ 31-40 „	18 „
„ 41-50 „	39 „
„ 51-60 „	18 „
„ 61-70 „	11 „

The durations of the policies were :—

Under 1 year	1 case.
1-5 years	15 cases.
6-10 "	25 "
11-15 "	18 "
16-20 "	18 "
21-25 "	7 "
26-30 "	3 "
31-35 "	1 case.

The number of years between infection and death :—

1-5 years	3 cases.
6-10 "	8 "
11-15 "	13 "
16-20 "	17 "
21-25 "	18 "
26-30 "	10 "
31-35 "	9 "
36-40 "	3 "
41-45 "	4 "

The average age at death of 88 policy-holders who gave a history of syphilis was 47·5 years. The average duration of their policies was 11·92 years, and the average length of time between infection and death 21·5 years. The average age of those policy-holders who, judging from their causes of death, probably had syphilis was about 45 years, and the average duration of insurance 10·5 years. On the other hand, the average age at death of all the other policy-holders in the same period of time was 48·5 years, and the duration of insurance roughly twelve years.

The average age at death of 86 cases of general paralysis was 45·5 years, with an average duration of insurance of ten years.

1-5 years	17 cases = 19·7 per cent.
6-10 "	29 " = 35·5 "
11-15 "	26 " = 30·2 "
16-20 "	10 " = 11·8 "
21-22 "	4 "

The 18 cases of tabes were of an average age at death of 47 years and an insurance duration of sixteen years. The averages for the 17 aneurysm cases were 46 years at death and eleven years of insurance.

For purposes of comparison, under the total of 2,503 deaths were 20 per cent. from tuberculous causes, 12 per cent. heart-failure, syncope, and degeneration, 7·7 cancer, and 7·2 acute lung inflammation.

Gotha Company : 1,778 syphilitic histories, 487 deaths.

Ages	15-35 years	38 per cent.
"	36-50	"	86 "
"	51-70	"	61 "
"	71-90	"	40 "

Dr. F. Parkes Weber examined the causes of death of 500—of which 45 were females—consecutive claims on the North British and Mercantile Insurance Company, England. In only three instances was there a history of syphilis given by the proposer. One of these died at the age of 56 from vesical calculus, ulceration, and haemorrhage, another died aged 31 years from tetanus after fracture, and the third at 53 from shock after an operation for appendicitis.

There were thirty deaths which were more or less probably the results of syphilitic infection, due as follows :—

General paralysis, ages varying from 37 to 70.	.	.	.	10
Locomotor ataxia	.	.	.	4
Spinal cord disease	.	.	.	2
Cerebral haemorrhage or thrombosis under 50 years of age	.	.	.	5
Cardiac failure under 50 years of age: heart-stroke	.	.	.	7
Aneurysm	.	.	.	2

Dr. Weber considered that 18 of these 30 cases were due to syphilis, i.e. 3.6 per cent. of the total deaths. He thought that this was not too large an estimate, and that it was not improbable that syphilis may have had a share in a few other deaths than these 30, e.g. from cirrhosis of the liver. The causes of death of the 467 other claims would have been very interesting, for one could then see whether there were amongst them others in which it was possible that syphilis played some part.

If we assume that 20 per cent. of these 500 cases had had syphilis at one time in their lives, we have 18 deaths in 100 syphilitics, that is, 18 per cent. This percentage would have been higher if causes of death which might have been due indirectly to syphilis had been taken into consideration.

Dr. Byrom Bramwell, examining the returns of 3,658 deaths in the Scottish Widows' Fund in the seven years 1888-94, found 6 deaths from tabes, 52 from general paralysis, and 24 from aneurysm. He supposes that only 75 per cent. of the 58 deaths due to tabes and general paralysis, and 50 per cent. of those due to aneurysm, were the results of syphilis, that is, 55.5 deaths

out of a total of 3,658 deaths. Assuming that 20 per cent. of the total number of males who died had had syphilis—which he thinks is a high estimate—he finds that 7·5 per cent. of all the syphilitics who insured in the Fund died from these sequelae of the infection.

It may be pointed out that, in view of most recent statistics, Dr. Byrom Bramwell takes a low estimate of the frequency of syphilis as a cause of tabes and general paralysis, and probably of aneurysm. For the sake of argument, let us assume that 90 per cent. of the cases of tabes and general paralysis, and 75 per cent. of those of aneurysm, were due to syphilis (in all 68 cases), and we find that 9·3 instead of 7·5 per cent. of all the syphilitics died from the effects of the disease.

Again, Dr. Bramwell purposely did not take into account in this calculation the probability of some deaths from other brain and spinal lesions, or from liver and kidney diseases, or, more important still, deaths at an early age (below 40) from cardiac and circulatory diseases, being due to syphilitic causes.

Thus, in the report from which he obtained his information we find that in the same period of time there were 297 deaths from apoplexy. One of these occurred between the ages of 25 and 35, and 20 in the succeeding decennium; 41 deaths occurred before 50. There were 11 cases of tumour of the brain, 3 of disease of the brain plus epileptic convulsions, 3 cases of chronic myelitis, and 1 of spinal meningitis, as well as many other lesions less likely to be specific (the ages are not stated). The information about the heart and other organs is indefinite from our point of view.

Some of these deaths must have been due to syphilis, so, whilst Dr. Bramwell's figures are useful as an indication of the frequency of death from locomotor ataxia, general paralysis, and aneurysm amongst syphilitic persons, they underestimate, as he states himself, that from all syphilitic diseases.

Dr. Byrom Bramwell assumes that the expectation of life in each of the cases of tabes, general paralysis, and aneurysm which he included in his estimate would be shortened by at least eighteen years on an average, and this means that there would be a total

loss of 135 years amongst every 100 syphilitic persons who died from the three diseases. That is to say, that in every syphilitic person who insured in the Scottish Widows' Fund during the years 1888-94, the expectation of life was reduced 1.3 years as the result of syphilitic tabes, syphilitic general paralysis of the insane, or of syphilitic aortic aneurysm.

Audry, from a close consideration of the published experiences of many observers, and from his own observations, forms the conclusion that 14 or 15 per cent. of syphilitics die from their syphilis after a period of time which may exceed forty or fifty years. Further, that the mortality is powerfully influenced by treatment, age, climate, race, alcohol, &c. He believes that in France the mortality of syphilitics who have been properly treated, and who are young and temperate, ought not to exceed 4 or 5 per cent., whilst this proportion must be increased tenfold in older and intemperate people.

The conclusions of the foregoing Continental observers (excluding those of Audry) will hardly satisfy the majority of observers with our present knowledge of the sequelæ of syphilis. It is possible that further experience will alter our views of the effects of syphilis in producing serious disease in the circulatory, respiratory, digestive, and excretory organs, as much as they have been altered in the past twenty-five years in regard to the nervous system. At present, however, Runeberg's and similar opinions will not be accepted very widely. Much more likely estimates are those by Audry, Bramwell, and Weber.

The American insurance companies' collected experience of the insurance risks of 5,385 policy-holders who declared that they had had syphilis previous to their examination, but who were all accepted, and who therefore presumably were otherwise quite good lives, was as follows:—

<i>Age-periods.</i>	<i>No. of policies issued.</i>	<i>No. of deaths.</i>	<i>Expected deaths.</i>
15-28	1,117	45	42.8
29-42	3,291	232	172.5
43-56	909	107	69.8
57-70	68	13	12.8
	5,385	397	297.9

The mortality experience as related to the expectation (100) at these different age-periods was therefore :—

Age	15-28 years	105·1 per cent.
„	29-42	„	134·5 „
„	43-56	„	153·3 „
„	57-70	„	101·6 „
Average								<hr/> 133·3 <hr/> „

The deaths were not necessarily due to syphilis, but the fact remained that, for some reason, despite all care in selection, the mortality among those who had a history of syphilis was 33·3 per cent. above the expectation.

CONGENITAL SYPHILIS

Congenital syphilis rarely comes into consideration in life assurance matters, but if it is recognized in a young proposer it would debar from assurance. In adults signs of the disease under otherwise favourable circumstances need not necessarily prevent the issue of a policy.

CHAPTER XVIII

OPINIONS OF MEDICAL REFEREES

Mr. ARTHUR SHILLITOE declines cases under certain conditions :—

1. No case to be considered until at least three years shall have elapsed from the time of infection, i. e. two years' treatment and one year's probation free from treatment and all symptoms.

2. Proposers should be declined who wilfully attempt to mislead by misstatements as to facts.

3. Many cases will be found to have been treated in the early stages with iodides only ; these, equally with those which have been inefficiently treated with mercury, are amongst the worst risks. He would rather recommend a case with cutaneous gummata than one of these, especially as many of them are not so liable to lesions of vital parts. The stress of the disease falls on that system of the body which the individual has tried most severely.

4. Alcoholics and free livers are, of course, bad risks.

5. No case acquiring syphilis after 45 is to be recommended.

6. The family history, as regards neurosis and other hereditary taints ; the individual himself, the effects that attack and treatment may have had upon him, must be carefully considered.

7. All cases showing early implication of the nervous system, e. g. transitory paralysis, diplopia, epilepsy, &c.

Mr. Shillitoe believes that there are very many cases which we may safely recommend for assurance, our chief guide being the answer to the question—Has the case been efficiently treated, i. e. with mercury, for two years continuously, and reacted satisfactorily ? There must also have been a further period of one or two years with freedom from symptoms and all treatment, and the life must in all other respects be a good one.

Dr. De Havilland Hall thinks that every man who has had syphilis, whatever treatment he has had, is not so good a life as the

man who has not had syphilis. He would not take a syphilitic at an ordinary rate. He has been particularly struck with the incidence of syphilis on the larynx, and has seen a sufficient number of cases of death arising from laryngeal conditions as the result of syphilis to make him feel that syphilis is a disease which may kill comparatively early. No case should be taken under four, or possibly five, years from the infection, and at least for a year should show complete freedom from all syphilitic appearances.

Sir William Gowers has met with many cases in which what was supposed to be thorough early treatment was followed by later constitutional symptoms. He thinks that to allow treatment to have an influence, or a considerable influence, on the judgement of cases for life assurance is an error, and to allow continuous treatment to have an influence is a double error. Cases do occur in which thorough early treatment has been followed by later constitutional symptoms.

The two chief elements in causing loss are vascular disease, i.e. arterial disease, especially as affecting the arteries of the brain and heart, and possibly of the spinal cord in the earlier period, and general paralysis in the later period. The danger from tabes is much less than that from general paralysis.

In his opinion, every proposer who has had a chancre of any kind within the preceding five years should be rated up five years, and every man who has had any secondary symptom within five years should also be rated up five years.

Dr. Pye-Smith would not regard a proposer who had had syphilis as a first-class life; but would make anybody who had suffered from it pay a syphilitic rate, and would not recommend any one who was still suffering from any active manifestation of the disease for insurance. The cases he would have must be cured, and the rate added would be from five to seven years, according to age.

Dr. Pernet believes with Trousseau that involvement of the ocular apparatus means a serious attack of syphilis, and he considers that the history of syphilitic iritis or other eye trouble of luetic origin ought to exercise a certain amount of influence on the premium, and the candidate with that history should have

a certain number of years added. He points out that intra-urethral chancres may often be overlooked, and the discharge from them wrongly ascribed to gonorrhoea.

Dr. F. Parkes Weber would make five years' addition on a history of syphilis in the case of persons in ordinary health (and without any active syphilis) who apply for life assurance within five years of the last active sign of primary or secondary syphilis. But he feels very decidedly that there are certain cases who present themselves with primary or secondary syphilis in which assurance may be risked with a relatively moderate extra, even whilst there are still signs of disease on the applicant. Such cases are adults of 20 to 30 years of age, bodily and mentally well developed, who are without any detrimental family history of degenerative disease of the circulatory and nervous systems or of tuberculosis, and in whom there is no suspicion of intemperance in alcohol.

Dr. P. H. Maclaren says : ' Syphilis is an ailment which revels in exceptions ; but, as a rule, I believe, if a man having acquired syphilis is to suffer from the tertiary manifestations, he will exhibit the signs and symptoms of this form of the malady within four years of the normal termination of the disease, i. e. six years after infection. After these preliminary statements, and without reference to general mortality statistics, from which it is difficult to obtain accurate information, I would be inclined to classify for insurance purposes all syphilitics under the three following groups :—

' 1. If a man has been properly treated, the probabilities are that, provided he is of good constitution and habits, no complications will arise, and the expectation would be that he will go through life with scarcely more appreciable risk than one who has never had the disease.

' 2. If proposer has not undergone a sufficient course of treatment, and applies for insurance before the expiry of six years, and yet is not suffering from any tertiary manifestations, and is otherwise satisfactory, the chances are that he may escape the malign form, but a 10 per cent. extra should be charged until the expiry of the six years, and then reconsider the case.

‘3. When tertiary symptoms have developed, the proposal should be absolutely declined, because, while treatment may temporarily remove these, it cannot eradicate the tendency to recurrence ; and clinical observation has shown that those so affected rarely live beyond a term of ten years, and often much less where palliative treatment is wanting.

‘While my personal experience is almost absolutely favourable regarding the prognosis of the cases included in Class I, it is questionable, when the cases are looked at, with the interests of the offices perfectly safeguarded, if they should not practically be treated in the same way as those in Class II.

‘The chief points to be aimed at for the benefit of all concerned are unanimity of opinion and of action.’

Mr. J. A. Bloxam : ‘After twenty-five years’ personal experience in the treatment of syphilis, I cannot think that any man who has ever had syphilis can be rated as a first-class life. The mere fact of his having had syphilis at once places him in a second-class division. No case with any secondary symptoms is insurable, nor is any case with distinct tertiary lesions. Syphilis lowers the vitality of individuals, and any person who has had it is liable to tuberculosis, chronic irritations, cancer, and so forth. Therefore it is not possible to accept any man who has syphilis as a first-class life ; he should be taken with an addition to the premium.’

Dr. Byrom Bramwell does not think that any man who has had syphilis should be accepted as a first-class life, but, generally speaking, only with an extra. He is of opinion that, for the first ten years after the syphilis is contracted, a period of time in which aortic lesions and parasyphilitic diseases most frequently develop, the extra should be larger than during the second period of ten years, say six to ten years ; that for the next eleven years (provided that no further symptoms have developed), during which the risk of tertiary symptoms is much less, but still considerable for aortic and parasyphilitic lesions, the extra should be somewhat smaller, say from four to six years ; and that for the remaining period of life (provided that no further symptoms have developed) the extra should be very small, say two years,

or, in some instances, omitted altogether. Other circumstances than the mere fact that the proposer has had syphilis must be taken into account, and for the amount of extra each case should be judged on its merits. He attaches great importance to thorough and prolonged mercurial treatment, though even in such cases tertiary and parasymphilitic lesions sometimes develop. Consequently the extra should be considerably less in cases in which adequate mercurial treatment has been employed than in cases in which there has been inadequate treatment or none at all.

When the policy is a short-term endowment policy (for twenty years, terminable at 50 or death), the extra may be to some extent reduced, but this is a question more for the actuary, who must, however, remember that the main risk—the development of typical tertiary lesions of aortic and parasymphilitic lesions (general paralysis and tabes)—is very much greater during the first ten to twenty years after the syphilis is contracted than during the subsequent period of life.

Dr. Graham Brown: 'A man infected with syphilis has not a normal longevity, and should not be insured at normal rates.

'Assuming that he is otherwise in good health, that he is living a steady and temperate life, that the primary infection occurred at least four years before the date of the proposal, that no secondary symptoms have appeared for at least a year, and that there is evidence that thorough treatment was carried out, then I think a moderate loading—say five years in the case of a man of 30—should be applied, to be removed altogether at the end of fifteen years. If treatment has not been thorough, the loading would need to be correspondingly heavy.

'Any tertiary manifestations would make the life uninsurable, at any rate on the whole-life plan.

'Venereal sores, other than syphilitic, do not appreciably affect longevity. I take it, however, that for the purpose of assurance every sore is to be assumed to be syphilitic, unless proof to the contrary were supplied by the proposer or the medical man whom he consulted.

'I should like, in conclusion, to suggest the advisability of

preparing a special schedule for use in syphilitic cases, to be filled up by the medical man under whose treatment the proposer was.'

Sir Dyce Duckworth: If the applicant has been properly treated, say for two years, and shows no lesions, he should be accepted, other things being favourable in his condition, without any extra at all. He thinks that the majority of people who insure their lives in large and important offices in England are of a class who, if they become or have been syphilitic, can afford to be well treated. They are living wholesome lives, and there is but slight apprehension of their ultimately developing any further symptoms. Everything depends on the character, constitution, and habits of the individual you have to deal with, and whether he can get the best advice; for in such a case syphilis has a much greater chance of being recovered from than in the case of a poor man who is badly fed, intemperate, and imperfectly treated for his condition, or not treated at all.

Mr. Buxton Shillitoe would take a syphilitic applicant at ordinary rates if he had been under proper treatment for a couple of years or more, and had been without symptoms for six to twelve months, and provided the man were in good health. It is a very different thing if severe secondary symptoms are present. Such a case must be postponed for proper treatment, and then if free for twelve months after conclusion of the treatment he might be taken with a certain addition, varying according to his age, &c. A man with tertiaries in any special form ought not to be taken except on very extreme terms.

Dr. Colcott Fox wrote: A man who has had ordinary benign symptoms, and has undergone an adequate mercurial treatment, and is in good health, may be accepted after an interval of at least one year from the cessation of treatment and four years since infection. As symptoms appear in the vast majority of cases before 40, the life is more valuable after that age, unless the disease be contracted later in life.

Applicants with a history of severer infection, with relapses, or of inadequate treatment, or who have contracted the disease after 50, should only be accepted after a longer probation, and either at increased rates or for a limited period.

Those in whom syphilis has implicated the viscera or the mucous membranes, other than the tongue, in the tertiary period should be rejected.

Dr. Vivian Poore wrote : If a man has undoubted objective evidence of syphilis upon him, whether it is primary, secondary, or tertiary, he should be postponed if not declined. His general health and so forth must be taken into consideration. The history of syphilis and of its treatment is of doubtful value, but if a man gave a history of syphilis and he were healthy at the time of the proposal, Poore would look him over, and if he found no signs of disease would not be inclined to rate him up. If, on the other hand, he had undoubted evidence of syphilis upon him, he should either be postponed until the disease had vanished, or if his insurance was something urgent, he should be rated up very high indeed, especially if he were getting on in years.

Where there is a family history of malignant or nervous disease, its importance is increased to a certain extent if there is undoubted evidence that a proposer is syphilitic.

Dr. Hingston Fox, accepting Sir Douglas Powell's estimate that in 12 per cent. of syphilitic cases tertiary symptoms follow, and supposing that each one of these has his expectation of life shortened by ten years, thinks that at two years from infection an advance of three to five years would fully meet the risk. This advance might gradually decrease for those who applied at later periods down to a zero point at four or five years from infection, when a man showing good health might be taken clear. Each case in which less favourable evidence is forthcoming must be dealt with on its own merits.

Sir Jonathan Hutchinson takes a more favourable view of a syphilitic history.

The fact that a man has had syphilis ought not to weigh for anything at all in reference to insurance, and there are only a few exceptional cases in which severe complications had developed in which it should be taken into account. He has known amongst his private patients exceedingly few cases in which syphilis in any way seemed to prejudice life.

He has no strong impression that albumin in the urine of

syphilitics is a specially evil omen. He could easily count the cases in which it led to anything serious.

‘ If a man came to me with a primary chancre and nothing more, and he were in good health, and if I knew he was a man likely to submit to judicious treatment, I should say to any insurance office I was concerned with, “ Take this man by all means, there are no extraordinary risks : there are some little risks associated with him, but it is very probable he has a good sound constitution in other respects.” ’ The most important risks are run in the secondary period, but unless the case was quite exceptionable, unless there was something already revealed which showed that the patient had a risk which could be appreciated, he would not say that the mere occurrence of secondary symptoms would at all appreciably influence his estimate of the probability of life. In old age syphilis is a little more prejudicial than in earlier years.

Marsh (America) says : ‘ No case with a history of any primary venereal sore should be accepted until six months have elapsed after its first appearance. If, however, in the absence of all constitutional treatment, no other symptoms, such as glandular enlargement, eruptions, mucous patches, have appeared by this time, the applicant might be acceptable. If he has undergone any constitutional treatment a further postponement of six months after the termination of such treatment is necessary.

‘ No person with a history of syphilis is insurable, until a proper course of treatment and the lapse of at least six years from the date of infection.

‘ No person can be accepted who may have any history or evidence of tertiary manifestations.

‘ On the other hand, a person may be accepted who gives a history of constitutional syphilis, provided the original disease may not have been severe, that he shall have undergone a prolonged and satisfactory course of treatment, and a period of six years may have elapsed since the initial lesion, during the last two of which no relapses have appeared and no tertiary symptoms at any time.’

He cannot advise any rule for the acceptance of persons who have not been submitted to proper treatment ; such treatment

is to be regarded not only as a great safety against future dangers, but also as an assurance that, in the case of a possible reappearance of new symptoms, medical advice would be at once sought and followed.

Only persons up to the full standard of physique and health should be accepted.

Marsh further advises that the medical man who treated the proposer for the syphilis should be communicated with and asked for details of symptoms and treatment.

Greene (America): 'The Actuarial Society of America has shown that an excessive mortality is experienced, despite the careful selection exercised in the past; a much heavier death-rate, in fact, than in cases of past hip-joint disease or in non-abstinent liquor-dealers.'

Greene would under no circumstances advise that a straightforward policy be issued to any man who has a syphilitic history.

Endowment insurance might be safely granted in many of these cases, but to consider a syphilitic as having an equal chance with selected risks of reaching old age is to disregard the tremendous influence exercised by this disease in the incidence of other diseases, and its treacherous nature, as evidenced by the extraordinarily frequent and diverse outbreaks so familiar to every practising physician.

Hyde (America) (1898) says it is unfair to charge an extra risk for the insurance of syphilitic applicants otherwise in sound health and insurable. The syphilitic applicant for life insurance should be examined with a view, not so much to his syphilitic history, as to his condition with relation to all other items making up a satisfactory risk. In other words, if he has a good family history, a sound constitution, excellent habits, and has reached but not passed a satisfactory age, his expectation of life is probably that of other individuals in similar conditions without risk on account of syphilis.

The practice of Salomonsen's company, the 'Danmark', in the matter had been to accept no syphilitic case until four or five years after the last symptoms, and then to charge a premium of 10-15 per cent. in excess of the ordinary one. Specially

favourable cases might be taken at ordinary rates when ten to fifteen years had elapsed since infection.

In view, however, of Runeberg's, Tiselius's, and his own observations, Salomonsen altered the practice of his company in dealing with proposals from persons who had had syphilis. It seemed to him rational, however paradoxical it might appear at first sight, in the case of syphilitics who have carried out Fournier's treatment thoroughly, to insure them soon after the disappearance of the secondary symptoms (usually about two years from infection), but only on an endowment policy maturing between 40 and 50 years of age, and with a premium slightly (though not so much as heretofore, i. e. 10-15 per cent. in excess of the ordinary rate) increased.

In Kleinschmidt's opinion, every endeavour must be made in the medical examination to consider as thoroughly as possible the evidence of past syphilitic infection on the part of the applicant, and especially to emphasize careful attention to the early symptoms of general paralysis, tabes dorsalis, and diseases of the heart and vessels. Syphilitic applicants must prove previously to acceptance that they have undergone a rational treatment. Under such conditions, cases can be accepted in the fourth or fifth year after infection, if no relapses have occurred after treatment, and no trace of syphilitic sequelae remains. Whether they are to be accepted at ordinary or advanced rates depends upon the condition of the individual. Cases with any complication, such as a neurasthenic tendency or hereditary taint, and any who are alcoholic, can only be taken as under-average lives, or must even be refused altogether.

Blaschko considers that the importance of syphilis in regard to life insurance has been generally considerably underrated, and all applicants for insurance should be most carefully questioned and examined with the view to discover evidence of syphilitic infection.

A. The following classes of cases are to be declined :—

1. Syphilitics who come of tuberculous parents, who have passed through a suspected lung or larynx trouble, or who have at the time any suspicion of lung or larynx trouble.

2. Syphilitics who have a tendency to excess in alcoholic liquors.

3. Those who manifest any circulatory disturbance.

4. Those who have a hereditary nervous taint, who are themselves nervous or display any indications of an organic disease of the nervous system.

5. Syphilitics who have gone through any specific affection of the brain or spinal cord, even when this has been entirely cured before the date of application.

6. Those who have a weakened general constitution, or any other kind of disturbance of health which would not of itself require an extra premium.

7. Those who have not been treated at all or have been treated by quacks.

B. The following are to be postponed :—

1. All syphilitics in the first four years after the infection, to be postponed until the fifth year.

2. All syphilitics who at the time of application manifest any symptom of syphilis, to be postponed till six months after its disappearance.

C. All other syphilitics may be accepted, and this should be done without any extra premium being charged, for :—

1. If it becomes common knowledge that syphilitics will only be accepted at an increased premium, then a past infection will be even more frequently concealed than it has hitherto been.

2. The mortality tables which have formed the foundation for the present calculations of the insurance companies include syphilitic cases.

In individual cases it might be desirable not absolutely to decline cases which come under A 7, but to admit them at an increased premium.

Bayet refuses all applicants who show evidence of secondary or tertiary syphilis, and all those in whom the infection has been less than three years previously, even if no symptoms after the primary sore have appeared. In other cases the conditions of eligibility for assurance vary according to whether the applicant has or has not had treatment. In those that have been properly

treated he only accepts if three years have elapsed since the date of the primary sore, with freedom from symptoms for the last year. If there is any reason to suspect danger from tertiary lesions or parasymphilitic affections he will not accept a proposal until ten years after inoculation have passed and the applicant be in quite a good condition of health. Women he would take in six years under similar conditions.

He refuses all children with indications of hereditary syphilis.

Dr. Teleky, of the Austrian Phoenix Company, writes me: 'I refuse all those who have got syphilis in later years (over fifty), but the younger are accepted with an addition of age (10-15 years).'

CHAPTER XIX

CONCLUSIONS

FROM the evidence which has been brought forward in the preceding pages, it is obvious that a proposer who has had syphilis is not as good a risk for insurance as one who has not, other things being equal, and consequently that the premium for the former should be higher than for the latter class of insurers in the same type of policy. It would be only equitable if all companies adopted a uniform system in the matter of dealing with syphilitic proposers, so that a policy refused or offered at an increased rate by one company could not be taken at a better rate by another company whose officers thought less seriously of the risk run in accepting it. The objection to adding to the premium of every syphilitic proposer is that, in this case, information about the infection would be withheld even more frequently than it is under the present circumstances, and the only way to counteract this would be for all insurance companies to have a clause rendering the policy void or worth only a surrender value if a proposer, who did not declare previous syphilitic infection, died before the naturally expected time from a disease of syphilitic origin. The difficulty about such an arrangement, apart from the dislike of companies and proposers to conditional policies, is that of deciding definitely that death was due to a consequence of syphilis which had been acquired before the time of examination; for although the majority of observers believe that at least 90 per cent. of cases of locomotor ataxia and general paralysis are of syphilitic origin, it has not been definitely proved that the remaining 10 per cent. are. Again, whilst it is certain that many deaths which result from vascular disease at an early age are due primarily to syphilis, it would be difficult in practice to prove this definitely in individual cases. Consequently conditional policies are impracticable.

Before considering the question of extra premiums, we may state a few broad principles for dealing with syphilitic proposals

which might be adopted by all companies without detriment to their interests.

1. A syphilitic proposer is, *caeteris paribus*, not as good a life as a non-syphilitic proposer.

2. No syphilitic proposer who cannot bring forward satisfactory evidence of having undergone proper treatment should be accepted for assurance. It must, however, be remembered that those who have been treated properly are still liable to suffer later from sequelae, though not so liable as those who have undergone no treatment, or only an incomplete course.

3. It would be much more satisfactory if a special account of the symptoms and treatment of the proposer could be had from the private medical man who treated him.

4. Only those syphilitic proposers who are first-class lives in the matter of physical condition, hereditary history, and habits (absence of alcoholic excess especially) should be eligible at any rate of premium.

5. No syphilitic proposer should be accepted for assurance until at least three years have elapsed since the date of infection without any secondary or tertiary symptoms having appeared in the interval. An interval of six years is much safer in view of the fact that fatal tertiary lesions may occur in this period of time.

6. No proposer showing signs of the disease in any one of its stages should be accepted.

7. No proposer acquiring syphilis late in life (after 40) should be accepted.

8. Children of probably syphilitic parents, that is, parents who have died or who suffer from tabes or general paralysis, should not be accepted unless born before the infection was acquired.

Extra Premium. Assuming that some extra premium should be charged, the calculation of it is a difficult matter. The tables used for estimating the premium for policies issued at ordinary rates are drawn up from the ages at death of healthy males, that is, males accepted for assurance at ordinary rates only, and not from the ages at death of any impaired lives. Many of

the 'healthy males' have died from illnesses directly or indirectly attributable to syphilis, e.g. general paralysis, tabes, and other nervous lesions, and diseases of the circulatory organs and other viscera; for the possible consequences of syphilis were not appreciated so fully in the days when the data for the healthy males tables were being provided, and a previous history of syphilis was not asked for keenly, or, if obtained, thought to depreciate the value of a proposal. So, many syphilitic proposals must have been accepted at ordinary rates, and consequently enter into the statistics from which the healthy males tables have been calculated.

Theoretically, then, the premiums charged for healthy proposers ought to protect the insurance companies from loss, if a syphilitic, otherwise a first-class life, be accepted at ordinary rates, provided that no larger proportion of syphilitics succeed in getting assured in the future than in the past. As a corollary to this, it follows that if the mortality experienced by syphilitics accepted at ordinary rates is above that of the general body of assured lives—and from the evidence reviewed in the foregoing pages this seems to be most probable—their inclusion will tend to depreciate the chances of life generally, and to increase, consequently, the premiums charged for non-syphilitic ordinary-rate lives.

It would be impossible to correct this inequitable weighting of non-syphilitics by new calculations from the old tables. The only way to try to balance things is to add to the premium of future syphilitic proposers, and with the system of bonuses or deferred bonuses, if the syphilitics die earlier than the non-syphilitics, the latter would get their own back in the increased bonuses which their longer lives would assure them.

As has been shown on previous pages, the amount of extra premium charged for syphilitic proposals varies even with those companies which consider an extra to be necessary.

Taking all things into consideration, it seems only fair that an extra premium equivalent to the addition of five years should be charged, under the most favourable circumstances, on a whole-life syphilitic proposal from a man under 30, and this number

of years should be added to if unfavourable circumstances of age, family or personal history be present in addition.

Policies with premiums limited to a certain number of payments, or terminable at 50, might be issued in favourable cases at ordinary rates.

Dr. Byrom Bramwell's 'sliding scale' seems to me to be quite sound.

E. M. Brockbaw

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THE SERUM DIAGNOSIS OF SYPHILIS

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CHAPTER XX

THE SERUM DIAGNOSIS OF SYPHILIS

AMONGST the great advances in the diagnosis and treatment of syphilis which have been made in recent years, probably none surpass in importance the serum diagnosis.

The long periods of clinical latency which specially characterize this disease, with the consequent danger of lulling the patient into a false sense of security, and the frequently terrible manifestations which may follow neglect of treatment, have made the management of syphilis a particularly difficult matter. To convince the patient that he is still suffering from syphilis is half the battle of persuading him to continue treatment when clinical signs are absent. It is in this that the Wassermann serum test has proved particularly valuable. Though it does not enable us absolutely to affirm the absence of syphilis, it affords us a clearer insight into the real condition of a patient who has at some time been infected with syphilis than we could ever obtain by reliance on clinical signs alone. It enables us to estimate more closely the relative values of different lines of treatment, and by affirming the presence of syphilis in clinically obscure cases it frequently indicates a line of treatment which might not otherwise be attempted.

Before describing the technique of the test it is necessary to explain briefly the terms used and the theoretical foundation on which it is based. To do so will require a short discussion of some processes of immunity.

Generally speaking, when a foreign proteid, e.g. pathogenic bacteria, toxin, cells or serum of another animal, &c., gains entrance, artificially or otherwise, into an animal's blood-stream, the invaded animal develops a resistance to the introduced proteid. A good example of this is the immunity which is

induced by an attack of typhoid fever or an injection of typhoid vaccine. Analysis of the immune animal's blood reveals the fact that substances which are antagonistic to the foreign proteid have appeared for the first time, or if they were present before have increased very markedly. These antagonistic substances are known generally as antibodies, and the foreign proteid whose introduction into the animal stimulated their production is known as antigen.

Antigen, therefore, is any foreign proteid the introduction of which into the body of an animal gives rise to the formation in that animal's blood serum of antibodies. We will discuss here only such antigens as foreign blood cells and bacteria, and amongst the antibodies to which they give rise only those which when mixed with such blood cells or bacteria as caused their production have the property of dissolving them. These antibodies are known as haemolysins or bacteriolysins, according to whether their respective antigens were foreign blood cells or bacteria.

After injecting such an antigen as the red blood cells of a sheep into a rabbit in suitable doses and at correct intervals, the rabbit's blood-serum develops the power of dissolving sheep's blood cells, causing the haemoglobin to diffuse out into the medium. Thus a suspension of sheep cells in physiological salt solution is turbid, and if allowed to stand the cells sink to the bottom, leaving the supernatant fluid clear and colourless. But if rabbit's *fresh* anti-sheep-cell serum is added to it in suitable quantities, and the mixture is incubated, it quickly becomes transparent and bright red, while no deposit forms.

Further analysis shows that if the same anti-sheep-cell serum is heated at 55° C. for, say, half an hour, or is allowed to stand for a number of days, it loses its power of dissolving sheep cells. If such heated, or stale, anti-sheep-cell serum is added to sheep cells no apparent effect is produced, even under examination with a microscope. Nevertheless the anti-sheep-cell serum does produce an effect on the cells, since if to the mixture is added any fresh unheated serum, which by itself has no effect on sheep cells, solution of the red cells (haemolysis) occurs.

It is clear from this that haemolysis is the result of two

substances acting on red cells, neither of which is able to act without the other. One disappeared when the serum was heated or was allowed to stand for some days, but is evidently present in every fresh serum. This is known as complement. The other, which was not destroyed by heating or on standing, but is not present in every serum, being developed by the injection of foreign blood cells, is known as amboceptor.

Amboceptor is specific to the antigen which stimulated its production. Thus if anti-sheep-cell amboceptor is added to the red blood cells of a horse together with fresh unheated serum (complement), no haemolysis results. The specific nature of amboceptor and the non-specific nature of complement are well illustrated by the analogy of Fischer. The blood cells are a highly intricate lock, their specific haemolytic amboceptor is the key which fits the lock, and complement is the hand which turns the key. Any key will not fit the lock, but any hand will turn the proper key when it is fitted.

For all practical purposes it may be said that in the process of immunization it is only the amboceptor, not the complement, which increases in quantity.

The blood serum of many animals contains naturally some haemolytic amboceptor; thus most fresh human sera will dissolve sheep cells, and the serum of some guinea-pigs will dissolve ox cells.

The interaction between an antigen, its specific amboceptor and complement results in the inactivation of complement. This was proved by the Bordet-Gengou phenomenon,¹ which is the theoretical foundation of the Wassermann test, and is briefly as follows. If an animal be immunized against a given bacterium (antigen), and its heated blood-serum (containing amboceptor which is specific to that antigen), the antigen, and any fresh serum (complement) be mixed together in *suitable* proportions and incubated at 37° C. for, say, half an hour, and if then the mixture be tested for the presence of complement, none will be found. The test for free complement will be suggested by what has already been written. It will be remembered that the addition of heated anti-sheep-cell serum to sheep's cells

produced no visible effect, but that the further addition of complement resulted in solution of the red cells (haemolysis). Obviously, therefore, a mixture of sheep's or other animal's blood cells and its specific amboceptor is a very convenient reagent to use in testing for the presence of free complement. A suspension of blood cells with their specific haemolytic amboceptor is known as a suspension of *sensitized cells*. If such a reagent be added to the above mixture of bacteria (antigen), their specific amboceptor and complement after incubation, no haemolysis will occur, proving the absence of free complement. If, however, bacteria and an amboceptor which is not specific to those bacteria (e.g. cholera vibrios and anti-typhoid serum) and complement be incubated together and the test for free complement (addition of sensitized cells) be applied, the haemolysis which results proves that an antigen will not bind nearly as much complement in the absence of its specific amboceptor.

It is necessary in such experiments as these to mix the respective ingredients in correct proportions, since, on the one hand, serum alone and antigen alone can inactivate a certain amount of complement, and, on the other, there is a limit to the amount of complement which can be absorbed by serum and antigen acting together. If, therefore, less complement is added than can be accounted for by either of the other ingredients acting alone, failure of haemolysis proves nothing; while if more complement is added than can satisfy the immune serum-antigen affinity, the excess will produce haemolysis, and mask the reaction.

From what has been said, it will be easy to understand how a given fluid can be tested for the presence of any proteid or, on the other hand, for any antibody. All that is required to test for a given proteid is an antibody to that proteid and some fresh serum (complement), and in testing for an antibody the requirements are the antigen and some fresh serum. If the complement is bound in the mixture of the tested fluid, known antigen, and complement, then the suspected antibody is present. Such a test for antibody can be applied to the diagnosis of bacterial diseases. For instance, in gonococcal arthritis, when the

patient's serum is incubated with gonococci and complement in suitable proportions the complement is bound. On the other hand, a test for antigen on these lines can be applied to the investigation of blood-stains or the analysis of meat mixtures. If, for example, it were suspected that a blood-stain was human in origin, an extract of the stain (antigen), some anti-human serum (antibody), and complement incubated together and then tested for free complement would show if the complement were bound, that the stain was either human or chimpanzee in origin. Similarly in the analysis of meat mixtures, an extract of the mixture is tested in turn with the antibodies to each of its suspected constituents.

Instead of the bodies of micro-organisms, Wassermann and Bruck² (1905) found that extracts of these could be used as antigen, and this led Wassermann and his collaborators, Neisser and Bruck,³ to conceive the idea of testing the serum of syphilitic monkeys for antibody to the *Spirochaete pallida*. Cultures of this micro-organism were not available, but the liver of an infant dead of congenital syphilis is generally so stuffed with *Spirochaete pallida* that it is practically a rich culture, and it was considered that a watery extract of such a liver would act as *Spirochaete pallida* antigen in the test. The result justified the hopes of Wassermann, Neisser, and Bruck. Syphilitic serum (believed to contain antibody to *Spirochaete pallida*), extract of syphilitic infant's liver in 0.9 per cent. salt solution (believed to contain *Spirochaete pallida* antigen), and fresh normal serum (containing complement) when incubated together in suitable quantities and then tested for free complement by the addition of sensitized cells, were found to behave in the same manner as in the Bordet-Gengou phenomenon, absence of haemolysis proving that the complement was bound. The application of the test to human serum quickly followed as a matter of course.

The experiments of Wassermann and his colleagues were quickly confirmed by others. It was found that the test is practically specific to syphilis and the Wassermann-Neisser-Bruck reaction became an established factor in the diagnosis of syphilis.

So far the reaction was conceived as a Bordet-Gengou phenomenon applied to the detection of *Spirochaete pallida* antibodies in the blood serum, and, *ipso facto*, to the diagnosis of syphilis. But it was quickly shown by Weygandt,⁴ and by Marie and Levaditi⁵ and others, that watery extracts of normal organs, though not so active, could be used in place of extract of syphilitic infant's liver in this test, especially in the testing of cerebrospinal fluid. An important advance was made when Landsteiner, Müller and Pötzl,⁶ Porges and Meier,⁷ and Levaditi and Yamanoichi,⁸ working independently, showed that alcoholic extracts of normal organs serve the purpose of 'antigen' in the Wassermann reaction equally as well as watery extracts of syphilitic infant's liver. Clearly this was a departure from the principles of the Bordet-Gengou phenomenon, because such extracts of normal organs could not contain true *Spirochaete pallida* antigen, and if they were not true antigen then the substance in syphilitic serum with which they united to bind complement could not be true antibody to *Spirochaete pallida*. The question whether such true antibody does exist in syphilitic serum will be discussed later. It is sufficient to state at this point that although the test as it is conducted in the great majority of laboratories (using an alcoholic extract of some solid organ as 'antigen') does not detect *Spirochaete pallida* antibody, yet for practical purposes it is specific to syphilis.

CHAPTER XXI

TECHNIQUE OF THE WASSERMANN REACTION

Preparation of the reagents. It will be understood from what has already been written that the requirements for the Wassermann test are as follows : (1) serum to be tested, (2) a serum containing complement, (3) an extract of some suitable solid organ, and (4) a suspension of sensitized cells, the haemolytic system which is required to test for free complement after (1), (2), and (3) have been incubated together. In addition to these, test-tubes, an incubator regulated to 37° C., pipettes, watch-glasses and a supply of fresh, sterile 0.85 per cent. salt solution are also required.

The technique employed by different workers may be divided broadly into two classes : (a) the original, and (b) modifications designed to simplify the test. By the original test is meant one in which the principle of the original technique in so far as the constituents (1), (2), (3), and (4) above are derived from different sources, is adhered to. Strictly speaking, most workers now employ a technique which is a modification of the original technique, though adhering to the above principle ; but under modifications is meant here those tests in which the worker relies on the tested serum containing the necessary complement and haemolytic amboceptor, or only the complement.

Original test. Preparation of the reagents. Serum to be tested. The blood for this may be drawn off into a Wright's capsule just as if required for a Widal reaction. But for a fair test it is necessary to take 1 c.c. of blood, and it is much easier and less painful to draw the blood from a vein at the bend of the elbow. A needle of fairly wide bore (such as is supplied with a 10 c.c. antitoxin syringe) is sterilized by boiling, or immersing it in a pot of olive oil which is heated till it just begins to smoke. A rubber band

is fastened round the upper arm of the patient so as to make the veins stand out well, and the skin over a prominent vein is sterilized by painting it with tincture of iodine, or a solution of iodine in chloroform (1 in 15). The needle is held about its middle with its bevel looking upwards and run into the vein. The blood is received in a clean test-tube. It is not necessary for the test-tube to be sterile, unless the serum has to travel for some days to a laboratory. In this case it is best to sterilize the test-tube by steaming it rather than by dry heat, since the blood-clot separates better in a steamed than an absolutely dry tube. The amount of blood which is drawn off is not very material, within limits; as it is easier to work with larger quantities one usually takes about 10 c.c. The blood is set on one side for an hour or two to allow the clear serum to separate. If the specimen has to be sent through the post to a laboratory it is by far the best practice to send only serum, since this does not travel well in contact with clot.

After the clear serum has separated its complement must be removed by heating it at 55° C. It is usually recommended to heat for half an hour, but I think that this is longer than is necessary. The serum loses some of its reacting power at a temperature of 55° C., and this loss increases with the time during which the serum is heated. As I have found that ten minutes in a water-bath at 55° C. is sufficiently long to inactivate 0.5 c.c. (the quantity I prepare for the test) of serum, I do not heat beyond this time. Another reason advanced for heating for half an hour is that unheated serum is itself anti-complementary. Heated serum is also anti-complementary to a certain degree, and it is necessary to make provision for this property in calculating the proportions of the respective reagents. As far as my experience goes, all sera are equal in anti-complementary power after ten minutes' heating of the quantity mentioned, so that heating for ten minutes does as much as heating for a longer time, viz. inactivates the natural complement, and places the sera on an equality as regards anti-complementary power; it has the advantage that it does not remove so much of the specific reacting substance. Browning and Mackenzie have pointed out that

sera which have stood for some days develop increased anti-complementary power, although they may have been heated previously. On this account the tested sera should be heated on the day of the test, whether they have been previously heated or not.

Wechselmann⁹ considers that the loss of reacting power which results from heating is due to interference by complementoid (inactivated complement) in the tested serum, and recommends removal of this substance by treating the serum with barium sulphate. His technique is as follows: to 0.9 c.c. of the heated serum is added 3 c.c. of 0.9 per cent. salt solution, and 0.5 c.c. of a freshly prepared emulsion of barium sulphate. The mixture is shaken, incubated at 37° C. for an hour, and then centrifugalized. By this method he obtained positive reactions with syphilitic sera which gave negative reactions to the ordinary test, and the method is recommended by Wassermann and others in cases where it is important to apply a more delicate test than is ordinarily necessary. As a routine test in laboratories where the workers' time is already fully occupied, it is too complicated. Some have recommended removal of the complement with barium sulphate, without previous heating, but this method does not appear to get rid of the variable anti-complementary power of the serum, and is said to give non-specific reactions. The use of unheated serum without treatment cannot be recommended in the original test; it introduces two variables, the natural complement in the serum and the anti-complementary power already mentioned.

Complement is contained in practically every fresh serum, but some of these contain other substances which are disturbing to the test, and others do not contain much complement, so that for the original test it is the common practice to use guinea-pig serum. The blood can be obtained from the ear if required for only a few tests, or it may be removed by aspiration from the heart, but the simplest plan is to cut the animal's throat over a wide glass funnel leading into a suitable receptacle. The blood may be whipped at once and centrifugalized, or allowed to clot and the serum to separate.

Browning and Mackenzie¹⁰ do not recommend guinea-pig serum to be used till it is eighteen hours old, as they have found younger serum unduly sensitive to deviation. I have not experienced this, and prefer to use it when four to eight hours old from the clot, or any time the same day after whipping and centrifugalizing the blood. In its original state, complement deteriorates and becomes useless in a few days at room temperature or in the ice-chest, and this is a great disadvantage of the original test. To overcome it various devices have been suggested from time to time. Noguchi¹¹ suggested drying the serum on blotting-paper in a current of air, but although the power is retained fairly well in this way, the results are irregular, and Noguchi does not now recommend the method, except in exceptional cases. Friedberger¹² recommended the addition of pure sodium chloride to the guinea-pig serum, to the extent of 4 per cent. This method did not at first commend itself to workers, but more recently Alexander¹³ has obtained good results with complement preserved by adding to it sodium chloride powder in the proportion of 0.85 gm. salt to every 10 c.c. of the serum. When required for use the complement is diluted to 1 in 10 with tap water. Melkich¹⁴ claims to have kept complement in a fit condition for use in the Wassermann test for 2-2½ months by adding to it 6 per cent. of sodium chloride. I have little experience of these methods, but have recently tested complement preserved by salting and have found that the original power was retained up to a period of five weeks, the longest tried. When used in a series of twenty-one Wassermann tests, with a parallel series in which fresh guinea-pig serum was used, the behaviour was almost identical; but one serum, that of a treated syphilitic which had been continuously negative to a number of tests, was positive with two salted complements, and negative with the fresh complement.

Complement keeps well when frozen hard, and for the past three years or so I have found the following a convenient method of keeping it frozen: the serum is pipetted off into small capsules, such as are used for vaccine, and these, in turn, are placed in a test-tube, which is capped and immersed in a freezing

mixture within a vacuum flask, such as a Thermos. In a good flask it will keep frozen hard for two or three days, but should be examined daily, and the freezing mixture renewed as required. The serum should be kept frozen quite hard, or it will deteriorate.

Extract ('Antigen'). There can be no doubt that the quality of the extract determines that of the results obtained, and until a uniform source and method of preparing this ingredient has become established, the results obtained by different workers must differ in a certain proportion of cases. It is not so much in frankly negative and strongly positive serums that this happens, but in an important class of what may be described as borderline cases. These comprise cases of very early syphilis, latent, and well-treated cases, in which the reaction to the most delicate methods is not strong. A number of instances have been recorded where specimens of blood sera have been divided and sent to different laboratories for test. In one laboratory positive results have been obtained with sera which gave negative reactions in another, and this has led in some quarters to distrust of the test. More important than this, it is almost impossible under present conditions to compare the results of treatment obtained by different workers. One has only to test a batch of sera with a number of extracts prepared identically from various organs to find the explanation of this. With one extract a high proportion of positive results will be obtained, with another as many negatives, and so on. As will be mentioned, excellent work has been done recently in the direction of discovering a method of making extract which gives uniform results, and it is not too much to hope that before long the test will be standardized by this means.

As already mentioned, the extract was originally prepared by treating with salt solution the livers of infants dead of congenital syphilis. The organ was minced and shaken for twenty-four hours with 0.9 per cent. salt solution, containing 0.5 per cent. carbolic acid, in the proportion of 1 gramme of organ to 4 or 5 c.c. of salt solution. It was then decanted or filtered, preferably the former.¹⁵ Marie and Levaditi¹⁶ recommended mincing the liver, and then grinding it to powder with as little solution

as possible. It was then dried *in vacuo* over sulphuric acid and stored as powder. For use, 1 gramme of powder was extracted with 30 c.c. saline, just before it was required for the test. Although Plaut¹⁷ and some others still prefer watery extract, especially for the testing of cerebro-spinal fluid, the majority of workers prefer to use alcoholic extract. Watery extract requires syphilitic infant's liver, which may be hard to procure, and it is also very apt to deteriorate suddenly.

Serviceable alcoholic extracts can be prepared from a variety of organs, and appear to be very stable.

Many workers, notably Citron, Wassermann, and others, however, hold strongly that alcoholic extract of syphilitic liver is superior to that of normal organs, and the world of Wassermann workers may be said to be divided into two camps, those who use only syphilitic extract, and those who either lay no great stress on this point or actually prefer extract of normal organs. Some consider that autolyzed syphilitic liver acts the best, but, as Browning and Mackenzie¹⁸ have shown, extract of autolyzed organ is more anti-complementary than others, and is also haemolytic. One of these properties masks the other to a certain extent, and it is impossible to titrate such extracts satisfactorily. I have obtained as good results with extract of normal as with syphilitic infant's liver, and prefer healthy organ to diseased, for the reasons advanced by Browning and Mackenzie.

Of organs which may be employed for making extract are the following : human liver and heart, ox liver and heart, guinea-pig's liver and heart, and rabbit's heart. Opinions are by no means unanimous as to which of these is the best, though, as will be mentioned, powerful evidence has recently been produced in favour of human heart extract, which has the added merit of being uniform. This is by no means the case with other organs.

The usual method of preparing an alcoholic extract is as follows : The organ is minced and then rubbed up in a mortar containing some broken glass, with four times its weight of 96 per cent. alcohol. The mixture is put into a bottle and kept

at room temperature, with frequent shaking, for twenty-four hours, after which it is filtered through fat-free paper. I have obtained good extracts by the following plan: The ground-up mixture of organ and alcohol is kept at room temperature for three days and at 37° C. for three days, being frequently shaken; it is then heated at 60° C. for an hour, and filtered through fat-free paper. The filtrate should be quite clear; on standing a deposit settles to the bottom of the bottle in which it is kept, and the extract should not be used till all the deposit has settled, i.e. for about a week.

The above are the simplest methods of preparing extract, and generally prove quite satisfactory. Some extracts prepared in this way, especially if autolyzed organ is used, may have to be rejected, because they are haemolytic, and by themselves absorb an undue amount of complement. It has been found by Noguchi and Bronfenbrenner,¹⁹ and others that these undesirable properties, especially the haemolytic, are due to the presence of substances which are soluble in acetone, and some workers use acetone in the preparation of their extracts. The details of some of these methods, which are rather more complicated, are given in the Appendix.

Sometimes, although it has no undesirable qualities such as the above, a simply prepared extract does not act very powerfully with syphilitic serum. Such an extract, of course, would give an undue proportion of negative reactions, and would ordinarily be discarded.

Following on the observation by Browning, Cruickshank, and Mackenzie that syphilitic sera deviate more complement in the presence of lecithin and cholesterin than with lecithin alone, Sachs²⁰ recommended the addition of cholesterin to the extract in the form of a 1 per cent. alcoholic solution. According to Sachs, the correct amount, which is found by trial, varies from 0.3-0.5 c.c. of cholesterin solution for every 5 c.c. of crude extract. In common with numerous other workers, I have found that the addition of cholesterin has improved the deviating properties of all the crude extracts to which I have added it, and up till quite recently used human heart extract,

to which 1 per cent. cholesterin was added in the proportion of 0.5 c.c. cholesterin to 5 c.c. extract.

Sachs's work was the main foundation of some valuable observations by McIntosh and Fildes, which promise to solve the problem of finding an extract which is simple to prepare, uniform in regard to the properties of each supply manufactured, and powerful in deviating properties.

Michaelis²¹ first advocated the use of human heart extract, and this has been found to be always uniform in the Statens Seruminstitut, Copenhagen, by Thomsen and Boas,²² though the latter believe that human heart extract becomes unstable with age, and make a fresh supply each week. The minced organ is there shaken with absolute alcohol in the proportion of 1 of organ to 10 of alcohol. McIntosh and Fildes²³ carried out an extensive test of various extracts, including alcoholic extract of syphilitic infant's liver prepared under the direction of Wassermann and Meier for the market, alcoholic extract of human heart, with and without cholesterin, and the lecithin-cholesterin mixture of Browning, Cruickshank, and Mackenzie.²⁴ As a result of tests of these extracts with over 500 serums, of which over 300 were syphilitic, they concluded that a heart-cholesterin extract made in the simple manner described below is superior to heart or syphilitic liver extract, or lecithin-cholesterin. Further, 24 heart-cholesterin extracts prepared in this way behaved exactly identically as regards anti-complementary power, and deviating properties with syphilitic serums. The extract is prepared as follows: The fat having been cut away, the muscular portion of the left ventricle is minced and ground for one minute with absolute alcohol (1 gramme of heart to 9 c.c. of alcohol) in a mortar, with clean sand. The mixture is shaken in a mechanical shaker for 1½ hours, and then filtered. In their first paper on this subject, McIntosh and Fildes recommended the addition of a 1 per cent. alcoholic solution of cholesterin (Kahlbaum) in the proportion of 4 parts of cholesterin solution to 5 parts of heart extract, and fresh extract was prepared every month; but in a more recent article,²⁵ the proportions are two of cholesterin solution to three of heart extract, and the extract should keep

in the ice-chest for six months. Walker and H. Swift ²⁶ have repeated the work of McIntosh and Fildes in principle. They prepared their heart extract by adding one gramme of minced heart muscle to 10 c.c. absolute alcohol, and the mixture was placed in the incubator for two to three weeks, being shaken daily. They obtained slightly better results by adding cholesterin directly to the crude heart extract than by adding it in the form of alcoholic solution. The strength of cholesterin in the finished product was 0.4 per cent., which compares with 0.44 per cent. in the original extract of McIntosh and Fildes. They found that human heart extract prepared in this way was slightly less sensitive than guinea-pig heart extract containing 0.4 per cent. of cholesterin, but that it was superior to ox-heart, guinea-pig liver, and normal foetal liver extracts containing 0.4 per cent. cholesterin, as well as to an alcoholic extract of syphilitic infant's liver containing 0.25 per cent. of cholesterin, an ether extract of dried human heart prepared after F. Lesser's formula and the extract of Wassermann and Meier tested also by McIntosh and Fildes. Both the two latter extracts were purchased from the firms responsible for their manufacture. They agree with McIntosh and Fildes regarding the uniformity of human heart cholesterin extracts, since three such behaved identically in their hands. Curiously, however, the extract prepared by Walker and Swift seems to have been less anti-complementary than that of McIntosh and Fildes, since in the first case not less than 1.2 c.c. of a 1 in 6 dilution was required to deviate 2 minimum haemolytic doses of complement when acting alone, and the second required only 0.8 c.c. of a 1 in 8 dilution to deviate $2\frac{1}{2}$ m.h.d. of complement, the quantity of test cells being the same. Possibly the difference may be accounted for by the different methods of preparing the crude heart extract employed by each. A short experience of extract prepared according to the method of McIntosh and Fildes has shown me that its anti-complementary power is as stated by them. I have also found it better than an extract prepared according to the directions of Sachs. More recently Kolmer, Laubaugh, Casselman, and Williams ²⁷ have confirmed

the above observations, and conclude that extracts may be classed according to the following order of merit: human, pig, and ox hearts and liver from the same sources, each with the addition of 0.4 per cent. cholesterin; alcoholic extract of syphilitic infant's liver, Noguchi's acetone insoluble fraction, alcoholic extract of normal heart, Kolle and Stiner's acetone soluble extract, and alcoholic extract of normal liver.

Artificial Extracts. Many chemical substances will deviate complement when incubated with syphilitic serum. Amongst these are lecithin, oleate of soda, taurocholate of soda, glycocholate of soda, and oleic acid. Sachs and Rondoni suggested that a combination of some of these would work in place of crude extract, and be more uniform. Their artificial antigen was found, however, to be not so good as crude extract, and no more uniform. Of all artificial preparations, I have found the ox-liver lecithin and cholesterin mixture of Browning, Cruickshank and Mackenzie to be the most reliable. The details of its preparation are given in the Appendix.

The Haemolytic System. This is a suspension of red blood-cells sensitized by the addition of the heated serum of an animal which has been immunized against those cells. For the original test it is not very material what variety of blood-cells is used. Most workers use sheep's, which are probably most convenient to obtain. Browning and Mackenzie²⁸ use ox cells, and Noguchi²⁹ claims advantages from the use of human cells. Whatever variety of cells is chosen it is necessary to immunize some animal with them, and the most convenient is rabbit. For the sake of convenience we will describe the technique when sheep's cells are used.

The blood can be obtained from the jugular vein, but is usually obtained at the slaughter-house. It may either be received into a 1 per cent. solution of citrate of soda in physiological salt solution or into a bottle containing a number of glass beads. The bottle, &c., should be sterile, and it is best to collect the blood after the sheep has bled for some time, as the first blood to flow must wash down many micro-organisms from the wool. If beads are used, as soon as the bottle is half-full it is stoppered and vigorously shaken so as to whip the blood in it.

It is best to keep the blood in the bottle and to wash it as required for the test or for immunizing purposes. As a rule it keeps good in the cold for three or four days. For use it is necessary to remove the serum from the blood. The blood is placed in a centrifuge tube, with an equal quantity of 0.85 per cent. salt solution, and spun till the cells are all deposited. The clear supernatant fluid is removed and replaced with salt solution, and this operation is repeated not less than five times. After the last washing the supernatant salt solution is removed and the deposit suspended in salt solution so as to make of it a 6 or 10 per cent. suspension. The strength of the suspension which is used in the test is 3 or 5 per cent., according to the practice of the individual worker, and this is obtained by mixing the 6, or 10, per cent. solution with an equal quantity of a suitable dilution of haemolytic amboceptor. For titration of haemolytic amboceptor (see later) the strength of the suspension is made 3 or 5 per cent. at once.

To obtain the haemolytic amboceptor a rabbit is injected repeatedly with washed sheep cells. It is best to immunize a number of rabbits at the same time, since some may die, and in any case rabbits vary very considerably in their response to the injections—some rapidly producing a potent serum and others the reverse. The injections may be made intravenously (into the marginal vein of the ear), intraperitoneally, or subcutaneously. For intravenous injections it is not advisable to give more than 2 c.c. at a time, and if the suspension is too strong (e.g. 50 per cent.) the rabbit may die suddenly about the fourth or fifth injection. I have obtained excellent haemolytic amboceptor by giving six intravenous injections each of 2 c.c. of a 5 per cent. suspension at weekly intervals. As a rule intraperitoneal injections should be stronger and in increasing doses, 2, 5, 7, 10, and 15 c.c. at weekly intervals, though Boas obtains powerful amboceptor by giving intraperitoneal injections of 1, 2, and 4 c.c. at intervals of 3–4 days and bleeding three days after the last injection. Subcutaneous injections are apt to result in abscesses, but, these avoided, a potent serum can easily be obtained in this way.

After a few weeks the rabbit's serum should be titrated for haemolytic amboceptor in the manner to be described, and when sufficiently potent (usually about ten days after the sixth injection) the rabbit is bled to death. The blood can be collected in various ways, of which the most convenient are the following.

Under ether anaesthesia the skin is reflected from the front of the chest, and after searing the site of the proposed puncture with a glass rod, the point of a chambered pipette is run into the right heart. The blood is aspirated into the chamber of the pipette, which is emptied into a sterile flask. Or the blood may be drawn off with a syringe, or through a needle and rubber tube attached to a vacuum flask. When as much blood as possible has been obtained in this way, the chest is opened, the heart and lungs removed, and the remainder of the blood and clot transferred from the thoracic cavity to the flask. Another method which works excellently is to expose the carotid and insert a canula, or strip it down as far as possible after ligaturing it in two places above. In the latter case the end is turned into a sterile test-tube and snipped with a pair of scissors.

The blood may be whipped and centrifugalized or set on one side for twenty-four hours before the serum is removed, but when it has clotted the clot should be separated from the sides of the tube, or flask, in which it is contained, so as to allow it to shrink properly.

It is convenient to bottle the clear serum in 1 c.c. vaccine ampoules. Every care should be taken to prevent contamination. After bottling, the complement should be removed by heating the serum for half an hour at 55° C. The serum will maintain its potency for many months, but should be kept in the ice-chest.

CHAPTER XXII

TECHNIQUE OF THE WASSERMANN TEST (*Continued*).

Standardization of the Reagents. It must be remembered that extract alone and serum alone, as well as normal serum in combination with extract, will deviate a certain amount of complement. The distinguishing characteristic of syphilitic serum is that in combination with extract it will deviate more complement than any of these. Another point to remember is that some syphilitic sera, especially those of well-treated cases, will not deviate much more complement than will normal sera under the same conditions. It follows from this that the proportions which the respective ingredients bear to one another in the test must be such that, on the one hand, no normal serum will react positively nor, on the other, an undue proportion of syphilitic sera give a negative reaction. On this account, after fixing arbitrarily the amount of the patient's or control serum to be used in the test, it is necessary to estimate quantitatively the strength of each of the other reagents, and from the information thus obtained to fix the amounts of these to be used.

In describing my own technique, I propose to make a departure from the usual practice of expressing values in cubic centimetres and fractions thereof, by speaking of volumes in varying dilutions. Thus, if in the usual nomenclature the minimum haemolytic dose of complement for 1 c.c. of sensitized cells were found to be 0.02 c.c., I should describe it as 1 volume of a 1 in 50 dilution for 1 volume of sensitized cells, or, briefly, as 1 in 50. Since it is the proportions which matter, and not arbitrary quantities, this amounts to the same thing. The size of the volume does not matter, within limits. In the practice of most workers it is either 0.5 c.c. or 1.0 c.c., but in my own practice, chiefly for the sake of economy, I have fixed the volume at about 0.12 c.c. Actually, it is the size of a drop delivered by a pipette made after the plan suggested by Donald (see below).

A fairly large number of capillary pipettes are graduated with mercury to measure this amount, and are used chiefly for the measurement of undiluted sera. Whenever practicable, the volume is delivered by a Donald automatic pipette. As will be seen later, the Wassermann test involves the addition of equal quantities of the same substances to numbers of test-tubes. This applies to sensitized cells, complement, extract, and salt solution. This otherwise laborious and eye-straining operation is saved by the use of an automatic pipette. The most satisfactory and easily made pipette of this kind is that devised by Donald.³⁰ It depends on the principle that at a delivery rate which does not exceed one drop per second, the size of the drop is practically constant and determined by the outside diameter of the delivery tube. The apparatus I use consists of a separator funnel, to the mouth of which is connected by means of a short piece of rubber tubing a short piece of quill tubing which is throttled at its upper end. By cutting short lengths from the same piece of quill tubing, delivery nozzles can be made for each of the pipettes in use, each of which will then deliver drops of practically equal size. To obtain drops of definite size, the delivery nozzle should be gauged, as recommended by Donald, by means of a Starrett Morse drill and wire gauge, which measures diameters of from 5.79 mm. to 0.34 mm. For still smaller diameters a wire draw-plate should be used, and for larger, the Columbia vernier gauge. An idea of the size of drops of distilled water delivered by a tube of given diameter may be gathered from the fact that, as measured by Donald, a nozzle measuring 14.5 mm. in outside diameter delivers drops of 0.25 c.c., while nozzles measuring respectively 0.34, 0.366, 0.406, 0.457 mm. (Morse gauge, Nos. 80, 79, 78, and 76) deliver respectively 131, 122, 112, and 101 drops per c.c. The mouth of the dropping nozzle must, of course, be quite clean, and Donald recommends in gauging to cut the tube off at the upper surface of the gauge plate so as to avoid contact with greasy matter on the plate. Donald's principle is applied by Fildes and McIntosh to the measurement of serum. They calibrate their pipettes by passing them through a hole in a wire gauge plate,

and cutting them off flush with the plate when they are held firmly. No. 53 in a Stubbs wire gauge plate gives a pipette which delivers drops of 0.025 c.c., or 4 to 0.1 c.c.

Using such small quantities of reagents, the various tests can be carried out in test-tubes measuring 5×1 centimetre. Instead of the usual type of incubator, it is very convenient to have a water-bath fitted with trays into which the test-tubes are slipped.

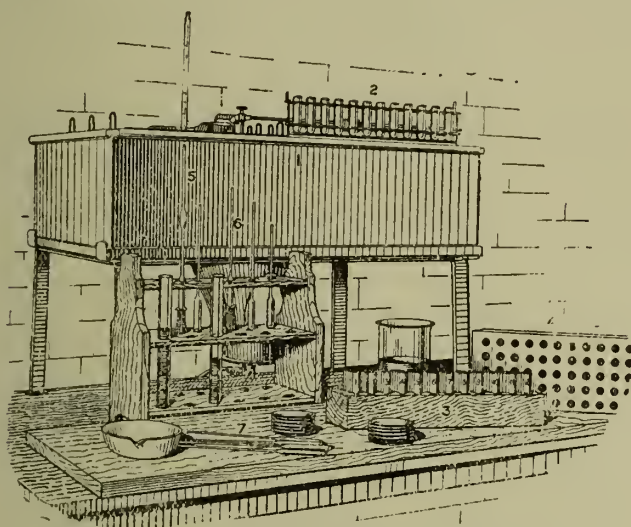


FIG. 1. Apparatus for the Wassermann Test.

1. Thermo-regulated water-bath.
2. Test-tube rack to fit into water-bath.
3. Test-tubes arranged in block of wood.
4. Block of wood suitable for test-tube stand.
5. Chambered pipette to measure four volumes.
- 6 and 7. One-volume capillary pipettes.

Titration of Haemolytic Amboceptor. To ascertain the minimum amount of rabbit's anti-sheep-cell serum which is sufficient to haemolyze completely a volume of sheep cells with the help of an excess of complement, a number of small test-tubes are set out in a row, and into each is placed one volume of a 3 per cent. suspension of the washed sheep-cells deposit. A series of dilutions of the anti-sheep serum is prepared, e.g. 1 in 125, 250, 500, 750, 1,000, 1,500, 2,000, and from each of these dilutions in turn a volume is taken and added to the sheep cells in one of the tubes, so that the row of tubes now contains a series of equal quantities

of sheep cells in contact with varying amounts of haemolytic amboceptor. After half an hour one volume of a 1 in 10 dilution of fresh guinea-pig serum (containing complement) is added to each of the tubes, and all are placed in the incubator at 37° C. The tubes are shaken about every ten minutes, and the reading is taken at the end of an hour. The tube is sought which contains

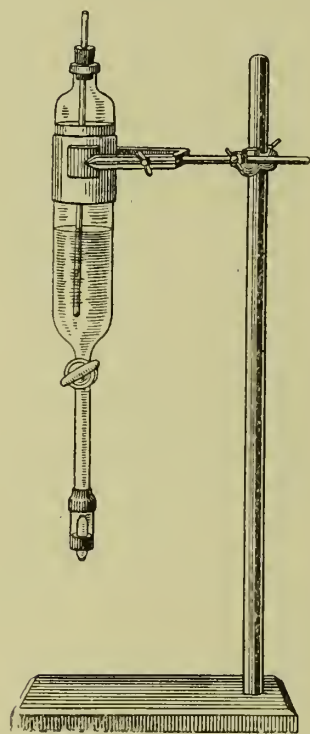


FIG. 2. Automatic, dropping pipette; after Donald.

the smallest amount of amboceptor, and in which there is complete haemolysis. The dilution of amboceptor serum in this tube represents the minimum haemolytic dose (M.H.D.) of the titrated amboceptor. It is not advisable to work with an amboceptor with a lower titre than 1 in 400. An excess of complement is used since one M.H.D. of amboceptor will not effect complete haemolysis when working with one M.H.D. of complement, and, within limits, the larger the amount of amboceptor with which the cells are sensitized, the smaller the M.H.D. of complement. This is mentioned here as it affects the question of the amount of amboceptor to use in sensitizing the cells for the titration of complement and for the test itself.

For sensitizing the cells some workers use $2\frac{1}{2}$, others 4 M.H.D., and still others larger quantities of amboceptor. Whatever quantity is to be used in the test proper must be used in titrating the complement. Since in the test proper the cells come into contact with a small but variable amount of haemolytic amboceptor which is present in the human serum, I have always considered it better to sensitize the cells beforehand with a large amount of amboceptor, so that in the test proper the M.H.D. of the complement as ascertained by previous titration will not

be affected by the additional amboceptor in the tested sera. For this reason I sensitize the sheep cells with not less than 5 M.H.D. of haemolytic amboceptor.

To make up the sensitized cells for titration of complement and for the test, assuming that 20 c.c. of sensitized cells are required, and that the M.H.D. of amboceptor is 1 in 1,500, 10 c.c. of a 1 in 150 dilution of the amboceptor is prepared and added to an equal quantity of a 6 per cent. suspension of sheep cells, making 20 c.c. of a 3 per cent. suspension of cells in a 1 in 300 dilution of amboceptor.

Amboceptor is very stable, and need not be titrated more often than once in about three months.

Titration of Complement. Complement must be titrated each time the test is performed, to ascertain the amount to be used.

The titration is done in a similar manner to that employed with amboceptor. A series of tubes is laid out and into each is placed one volume of a varying dilution of guinea-pig serum, e.g. 1 in 10, 20, 30, 40, 60, and 80. To each is then added one volume of sensitized cells prepared as above, and two volumes of salt solution, to make the bulk the same as in the test proper. The mixtures are incubated for half an hour and at the end of this time the tubes are examined. As in the titration of amboceptor, the tube containing the smallest amount of complement and in which haemolysis is complete is sought, and the amount of complement in it is noted as the M.H.D. of the complement.

The amount to be used in the test varies with different workers. Browning and Mackenzie use, as a minimum amount, 5 M.H.D. plus the number of M.H.D. which the serum alone and the extract alone will absorb. This seems excessive and likely to give an undue proportion of negatives, especially with the serum of well-treated cases. McIntosh and Fildes use $2\frac{1}{2}$ M.H.D., and Thomsen and Boas the smallest amount which gives complete lysis of the sensitized cells after incubation with the extract. For example, if the M.H.D. were 0.05 c.c. when acting alone, it would be about 0.08 c.c. after incubation with extract, and this quantity would be used in the test. This method of fixing the quantity of complement by its titre is better than that

originally employed, and still common, of using an arbitrary quantity of complement, e.g. 1 in 10 or 1 in 20, since, as Browning and Mackenzie³¹ have pointed out, the titre of complement in guinea-pig's serum varies so that if an arbitrary amount is used the serum-extract combination may on one occasion be required to deviate 6 and on another only 3 M.H.D. of complement. I now use, as a minimum, 3 M.H.D. of complement. For convenience, if lysis is complete in the 1 in 60 tube, the amount used in the test is one volume of 1 in 20, and if quite complete in

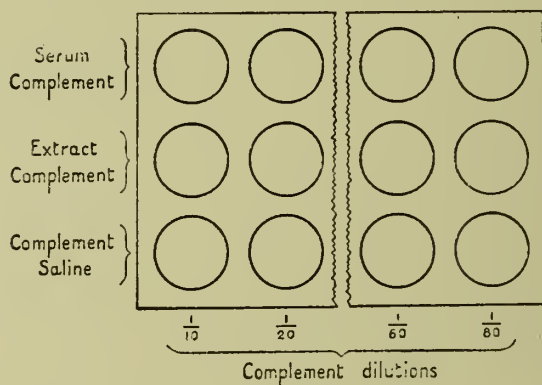


FIG. 3.—Plan of arrangement of tubes for titration of complement and ascertaining the amount of complement absorbed by serum and extract respectively, when acting alone.

the 1 in 40 tube and almost so in the 1 in 60, the amount is fixed at one volume of 1 in 15. Besides this, minimum, amount of complement I set up the same serum and extract with larger amounts of complement, as will be mentioned in more detail when discussing the quantitative estimation of the reaction.

In addition to determining the M.H.D. of the complement, in order to guard against the employment of a complement which is hypersensitive to deviation, Browning and Mackenzie recommend that the number of M.H.D. complement deviated by the amount of extract and of serum, respectively, to be used in the test should be ascertained. I have usually followed this practice, but not to the extent of testing the auto-deviating power of every one of the tested sera. A convenient plan of carrying it out is the following. Two additional rows of tubes

are set out (Fig. 3), into each tube of one row is placed a volume of the extract diluted as it will be used in the test, and into each of the other row a volume of any of the sera to be tested, in the same dilution as will be employed in the test. Into each tube of each row is placed a volume of the guinea-pig's serum in the same varying dilution as in the titration for M.H.D. The mixtures are incubated for half an hour, and to each tube is then added one volume of sensitized cells. After incubation for half an hour longer the tubes are read. To take a common example of such a reading, when the M.H.D. of complement is 1 in 60, the highest dilution of complement in the extract row which gives complete lysis is 1 in 30, showing that the extract by itself has absorbed one M.H.D. of complement. In the serum row, using 1 in 5 serum, it is common under these circumstances to find that the tube containing 1 in 40 complement is the last to show complete lysis, showing that the serum alone has absorbed rather less than one M.H.D. of complement. It is not practicable in a large batch of tests to estimate the auto-deviating power of every one of the tested sera, and, in any case, in the test itself the serum is put up with the minimum amount of complement used in the test, so that any abnormal deviating power which may be displayed by a serum acting alone is guarded against.

As mentioned, Thomsen and Boas fix the amount of complement to be used in the test by a similar procedure. Using heart-cholesterin extract, McIntosh and Fildes do not find it necessary to test the autodeviating power of the extract against the complement for each batch of tests. They maintain that this is the same always. Apparently they do not believe in the varying sensitiveness of guinea-pig-serum complement, and I must say that in some hundreds of specimens of complement which I have used, I have found it very uniform in sensitiveness to deviation.

The *extract* may vary in its deviating power according to the manner in which it is diluted. It was pointed out originally by Sachs and Rondoni³² that if the dilution is done slowly the result is a more turbid emulsion, with greater deviating power, than when the dilution is effected suddenly. McIntosh and

Fildes³³ find, however, that in the case of heart-cholesterin extract the deviating power is rather greater when the extract is quickly diluted. They recommend that the extract be floated on the necessary amount of saline, and the mixture quickly shaken, or, more recently,³⁴ to put the extract in a large tube, and add saline suddenly. Probably the observation of Sachs and Rondoni applies more particularly to liver extracts. When

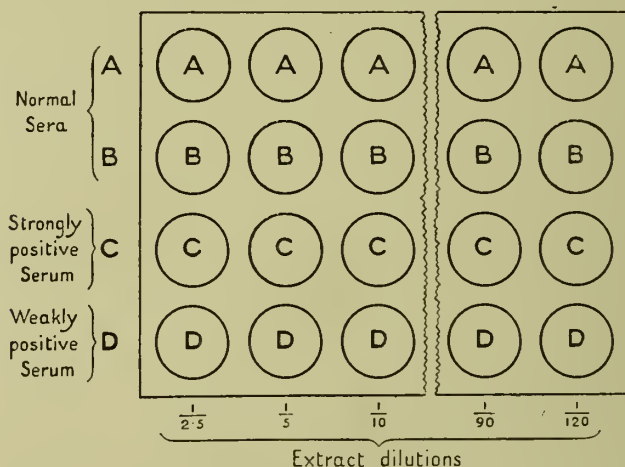


FIG. 4.—Plan of arrangement of tubes for titration of extract.

working with the latter I have usually diluted slowly, according to the method recommended by Browning and Mackenzie. The extract is floated on the top of the necessary amount of saline, just as urine is floated on nitric acid; the tube is set to one side for a time, and a white ring forms at the junction of the two fluids. The tube is then rolled between the hands, at first slowly till the salt solution has diffused into the extract lying above, and then more quickly. Finally, when the two fluids are almost mixed, the tube is inverted, and the result is a turbid emulsion. With heart-cholesterin extract I have diluted quickly according to the original plan of McIntosh and Fildes.

Before titrating the extract it is advisable to ascertain that it is not unduly haemolytic. To do this a volume of 1 in 5 dilution of the extract should be incubated with a volume of the suspension of cells and two volumes of saline for an hour. If

no haemolysis is apparent at the end of this time the extract is so far satisfactory.

The strength of the extract to use in the test is determined in many ways. Many workers use arbitrarily an amount which is equivalent to one volume of a 1 in 5 dilution. McIntosh and Fildes consider that in the case of a heart-cholesterin extract made according to their directions, the titre is so constant that it is not necessary to determine it for each fresh supply of extract. In a system where the amount of tested serum is 0.1 c.c., the complement, $2\frac{1}{2}$ M.H.D., and the quantity of cells eventually added, 0.5 c.c., they use 0.5 c.c. of a 1 in 15 dilution of a heart extract 3 + cholesterin solution 2 mixture. This is one quarter the amount which when incubated alone with $2\frac{1}{2}$ M.H.D. complement is just sufficient to inhibit haemolysis. Walker and Swift, using a heart extract containing 0.4 per cent. cholesterin in a system where the serum is 0.1 c.c., the complement, 2 M.H.D., and the amount of cells eventually added, 0.5 c.c., recommend 0.5 c.c. of a 1 in 10 dilution, or one quarter the amount which by itself is able to inhibit lysis. I have found the strength recommended by McIntosh and Fildes satisfactory when using their heart-cholesterin extract, but in working with other extracts, which certainly vary very considerably in value, have employed the following method, which is perhaps rather troublesome, but gives a good idea of the value of the extract. As the titration need be carried out only at the outset, and occasionally afterwards, the extra trouble is not of any great moment.

Four rows of test-tubes are set out (Fig. 4), and may be marked A, B, C, and D respectively; each row contains nine tubes. Into each tube of row A is placed one volume of a 1 in 5 dilution of the serum of a normal person. Into each tube of row B a similar amount of another normal serum. Into each tube of row C the same amount of serum which is known to give a strong Wassermann reaction (generally that of a florid secondary syphilitic). Lastly, into each tube of row D is placed the serum of a patient who gives a feeble Wassermann reaction. A series of dilutions of the extract to be tested is prepared, e.g. 1 in 5, 10, 15, 20, 40, 60, 90, and 120. Into the first tube of each row are put

two volumes of the 1 in 5 dilution of extract ; into the second, one volume of the 1 in 5 ; into the third, one volume of 1 in 10, and so on. In every tube is placed a volume containing 3 M.H.D. of complement, and, to make the bulk equal, a volume of saline is placed in all except the first tubes. After incubating for half an hour at room temperature and the same time at 37° C. a volume of sensitized cells is added to each tube, and incubation continued for another half-hour. The tubes are then examined, and the results vary with the quality of the extract. With a good extract all the tubes containing normal serum (Rows A and B) will show complete haemolysis, or, at most, there will be the very least deviation in the tubes containing two volumes of 1 in 5 extract. In the strongly syphilitic serum tubes (row C) lysis may be complete only in the tube containing 1 in 90 and 120, or even only in the last named. In the weakly syphilitic lysis may be partial in the tubes containing 1 in 10 and higher dilutions of extract. A poor extract may fail to deviate with a strongly syphilitic serum when in a dilution of 1 in 10, and yet show partial deviation with a normal serum when in a dilution of 1 in 5.

The strength of extract to be used in the tests is provisionally fixed at half the amount which just fails to deviate 3 M.H.D. of complement when in contact with a normal serum. This amount is then incubated alone with a number of varying dilutions of complement, just as was described in the titration of complement, to ascertain how many M.H.D. of complement it will deviate. If it deviates only one M.H.D. or less, the amount is so far satisfactory.

Finally, before taking it into use the new extract is tested alongside an accredited extract with 20 normal and 20 syphilitic sera.

CHAPTER XXIII

TECHNIQUE OF THE WASSERMANN TEST (*Continued*).

The Test. A normal and a known positive serum should be tested with the sera under examination. It is a distinct advantage to estimate the strength of the reaction. Here again the practice of different workers varies. Some consider that the strength of the reaction varies inversely with the amount of tested serum which will deviate a constant amount of complement with a constant amount of extract, and use varying quantities of tested serum. Generally this appears to be true, florid cases of syphilis reacting with smaller amounts of tested serum than well-treated cases; but sometimes a given amount of serum will give a negative and half this amount a positive reaction. Others vary the amount of extract, believing that the strength of the reaction varies inversely with the amount of extract which produces a positive reaction. This is certainly a useful method with modifications. In over 7,000 Stern tests I have never found a serum react with the smaller and yet fail with the larger amount of extract, and in treated cases the reaction with the smaller amount of extract is the first to die out. In the original test, following the practice of Browning and Mackenzie, I have always estimated the strength of the reaction by varying the amount of complement, on the principle that the stronger the reaction the more complement will be deviated. The results by this method, judging by over 10,000 tests, coincide very closely with clinical symptoms and the effect of treatment.

Assuming that a constant amount of tested serum and of extract respectively is to be used and that to estimate the strength of the reaction three different amounts of complement are to be used, a block of wood into which five rows of holes have been bored is taken and along the back row are set out the sera to be tested. The front four rows are filled with empty test-tubes, so that, as shown in the plan, there are four tubes in front of each

serum. Each serum is taken in turn, diluted to 1 in 5 with 0.85 per cent. salt solution, and one volume of this dilution is placed in each of the four tubes.

When every serum has been dealt with in this way, into every tube of the front three rows is put one volume of the diluted extract, and, to make the bulk equal in all the tubes, a volume of saline is placed in each of the fourth row tubes.

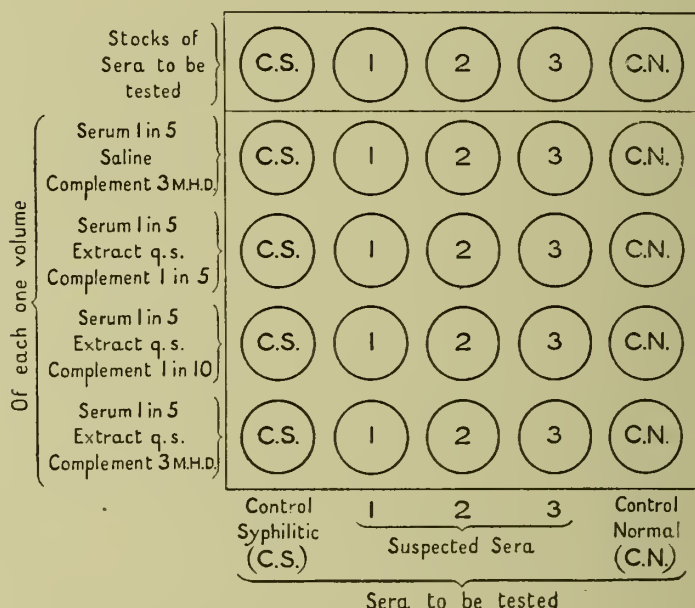


FIG. 5.—Plan of arrangement of tubes for the original Wassermann test when the strength of the reaction is determined by the amount of complement deviated. After preliminary incubation, to each tube is added one volume of sensitized cells.

The complement is next added. Into each tube of the front and fourth rows is put a volume containing 3 M.H.D. of complement (e. g., if the M.H.D. of the complement is 1 in 60, a volume of 1 in 20 is placed in each of these tubes). Into every tube of the second row is put a volume containing $4\frac{1}{2}$ –6 M.H.D. of complement (generally 1 in 10) and into each of the third row a volume containing 9–12 M.H.D. of complement.

It will be seen from this arrangement that the fourth row differs from all the others in containing no extract. It is a control

to show that the amount of serum in each test cannot by itself deviate the smallest amount of complement used in the test.

The tubes are shaken, allowed to stand at room temperature for half an hour, and then placed in the water-bath incubator at 37° C. for half an hour. Formerly it was the practice to place the tubes in the incubator at once, but a difficulty was raised when Jacobsthal³⁵ pointed out that in some cases binding of complement in the Wassermann test took place better at 0° C. than at 37° C. Guggenheimer³⁶ then found that in some cases it was better at 37° C. than at 0° C., and Thomsen and Boas³⁷ that in no case did binding occur better at 0° C. than at room temperature, but that in the majority of cases the reaction took place better at room temperature (or at 0° C.) than at 37° C. In a series of 207 serums which I tested at the same time by both these methods the results practically confirmed these conclusions. Of the total number tested, 35 were positive after preliminary incubation in the water-bath, as well as after standing at room temperature, and 158 were negative. Of the remaining 14 sera, 7 gave a positive reaction only after incubation at 37° C. and 7 only after standing at room temperature. The practical solution of the difficulty is that suggested by Boas, to incubate first at room temperature and then at 37° C.

At the end of this period to each tube is added a volume of sensitized cells, and incubation allowed to proceed. The tubes are shaken every five or ten minutes and if the normal control serum is placed last (as shown in the plan) it is sufficient to take the reading when this shows complete haemolysis. As a rule, the reading can be taken in half an hour.

The following are the rules to be observed in reading the results : (1) Failure of the normal serum test to show complete haemolysis in all its tubes entails rejection of the whole batch of tests. (2) Failure of any tube in the fourth row (control) to show complete lysis entails rejection of the test of the serum of which it is a control. These conditions being satisfied, (3) failure of haemolysis in each of the front three tubes (containing extract) devoted to the testing of any serum may be marked as strongly positive (+ + +). No haemolysis in the front two,

but lysis in the third row tube, not so strongly positive (+ +), and no lysis in the front tube only, with lysis in the other two containing extract, just positive (+). Incomplete lysis in a front row tube may be marked as doubtful (\pm or $\underline{\pm}$), and complete lysis in a front tube is returned as negative.

If the test is for diagnostic purposes it is a good plan to re-test the serum if the reaction is simply + to eliminate any possibility of an error in technique; this reaction, however, is good enough for a diagnosis. Doubtful reactions, \pm and still less so $\underline{\pm}$ should not be considered diagnostic. Such reactions are, however, generally given by very early or by well-treated cases of syphilis, and an early opportunity should be taken of testing the serum again, no treatment being administered in the meantime unless this is designed to provoke a definite reaction, as will be mentioned later.

When the results are read so soon as recommended above some difficulty may be experienced in deciding whether or no there is lysis in certain tubes since the cells have not sunk to the bottom. With experience partial lysis can be detected though the mixture is still turbid, but in case of doubt the tubes in question can be spun in the centrifugal machine.

I have found the method of conducting the Wassermann test which is described above entirely satisfactory in over 10,000 tests. Its great advantage is that it is economical in reagents and incubator space, and this is a consideration when large numbers of tests have to be carried out in one day, and when a class has to be supplied with materials for practice.

The following are the essential details of the original technique and that employed by some other workers. In each case the tested serum is heated at 55°C. for half an hour, and the haemolytic dose of amboceptor is ascertained by previous titration.

The original technique³⁸ was as follows: A watery extract of syphilitic infant's liver was prepared as already described, and the optimum quantity for use in the test ascertained by titration. The formula was :

Tested serum, 0.2 c.c.

Complement, 0.1 c.c.

Extract, 0.1-0.2 c.c.

Controls, 0.2 and 0.4 c.c. serum and 1 and 2 doses of extract respectively, were incubated alone with 0.1 c.c. complement; also a known normal and a known syphilitic serum with complement and extract as above. All the mixtures were made up to 4 c.c. with saline and incubated at 37° C. for an hour before the addition of 1 c.c. of a 5 per cent. suspension of sheep's red cells sensitized with 2 M.H.D. haemolytic amboceptor.

*Bruck*³⁹ (Breslau). An alcoholic extract of syphilitic infant's liver is used which has been tested with an accredited extract on 40 normal and the same number of syphilitic sera before being taken into use. The quantity is generally 0.2 c.c., the formula being

Tested serum, 0.2 c.c.

Complement, 0.05 c.c.

Extract, 0.2 c.c.

Before addition the extract is diluted according to the method of Sachs and Rondoni,⁴⁰ and the total quantity in each tube is made up to 4 c.c. Control tests of serum in single and double quantity and of extract respectively with the complement are also put up, and a normal and known syphilitic serum is included in the series.

After incubation for one hour at 37° C., to each tube is added 1 c.c. of a 5 per cent. suspension of sheep's red cells sensitized with 3-4 M.H.D. amboceptor.

All sera are tested also by Stern's modification (see p. 283).

*Statens Seruminstitut, Copenhagen.*⁴¹ The complement (fresh guinea-pig serum) is first titrated to ascertain its minimum haemolytic dose against a 5 per cent. suspension of sheep's red cells sensitized with 2.5 M.H.D. amboceptor. At the same time in each of another series of tubes containing similar quantities of complement is placed the dose of extract to be used in the test (0.2 c.c. of a freshly prepared alcoholic extract of heart muscle diluted with salt solution to 1 in 10). In each tube is also placed the necessary amount of haemolytic amboceptor and, lastly, 1 c.c. of a 5 per cent. suspension of sheep's red cells. Both series are incubated for 2 hours at 37° and the tube in each series sought in which haemolysis is complete with the smallest amount of complement. For example, without extract haemolysis may be

complete in the tube containing 0.05 c.c. complement, but in the extract series the smallest amount of complement which can effect complete haemolysis is 0.08 c.c. Assuming this to be the case, the main test is conducted as follows: Each tested serum is put up in varying amounts (0.2, 0.1, 0.05, 0.025, and 0.01 c.c.) in separate tubes. The volume in each is made up to 2.72 c.c., 0.08 c.c. complement is added, and 0.2 c.c. extract (diluted to 1 in 10). The tubes are shaken and, for the reasons mentioned above (see p. 273), incubated for 45 minutes at the room temperature and the same time at 37° C. The necessary amount of haemolytic amboceptor ($2\frac{1}{2}$ M.H.D.) is then added, the volume in each tube made up to 4 c.c., and 1 c.c. of a 5 per cent. suspension of sheep's cells then added. The tubes are shaken, incubated at 37° C. for 2 hours, and then placed overnight in the ice-chest for undissolved cells to settle to the bottom. The results are read by comparison of the supernatant fluid with a haemoglobin scale prepared in this way. Of the suspension of test cells a solution is made in distilled water by adding 4 of distilled water (representing the proportion of other ingredients in the test proper) to 1 of suspension. This represents 100 per cent. of haemolysis. Of this stock haemoglobin solution 9 c.c. plus 1 c.c. of distilled water makes a solution the colour of which corresponds to that of the supernatant fluid in a tube where there is 90 per cent. of lysis; 8 c.c. of the stock haemoglobin solution with 2 c.c. of distilled water makes a solution which matches with 80 per cent. of lysis, and so by making up successive quantities of 10 c.c. each, with less and less stock haemoglobin solution and more and more distilled water, a scale is made by which any degree of haemolysis in the Wassermann test-tubes can be matched. The rules for reading the results are as follows: Haemolysis ranging from 70 to 100 per cent. in a tube containing 0.2 c.c. of tested serum must be considered negative, but less than 60 per cent. of haemolysis in a tube containing the same amount of serum is read as positive.

*Fildes and McIntosh.*⁴² The 'antigen' is a mixture of human heart extract, 3, with 1 per cent. alcoholic solution of cholesterin, 2, mixed just before the test and diluted suddenly to 1 in 15 with

saline. The quantity used is 0.5 c.c. of this dilution, which represents one-quarter the amount which by itself can inactivate the quantity of complement used. The complement (fresh guinea-pig serum, used on the day it is drawn) is titrated against 0.5 c.c. of a 5 per cent. suspension of sheep's red cells sensitized with 3 M.H.D. amboceptor, and $2\frac{1}{2}$ M.H.D. complement (contained in 0.5 c.c.) are used. Immediately before addition to the tubes the diluted complement and extract emulsion are mixed in equal quantities, and 1 c.c. of the mixture is put into each tube requiring it. The tested serum is measured, as already mentioned, by drops, the drops being delivered by a capillary pipette of No. 53 gauge (Stubbs's wire gauge plate) held vertically. The size of each drop is 0.025 c.c. and the maximum quantity of serum used is 0.1 c.c. (four drops). The strength of the reaction is determined by using varying quantities of serum. In this case six tubes are required for the test of each serum. Into the first is put 0.1 c.c. serum and into the second, third, fourth, and fifth, respectively, 0.05, 0.025, 0.012, and 0.006 c.c., while the sixth (control) receives 0.1 c.c. serum. Into each of the first five tubes is then put 1.0 c.c. of the antigen-complement mixture and the sixth receives 1.0 c.c. of equal parts of complement and saline. Two extra tubes, controls for the whole series of tests, receive respectively 1.0 c.c. antigen-complement mixture and 1.0 c.c. saline-complement mixture. The mixtures are incubated in air at 37° C. for an hour, and to each is then added 0.5 c.c. sensitized cells, while 1.5 c.c. is put into a separate (control) tube. Incubation is continued for 20 minutes in a water-bath at 37° C. and the results read then or after standing for one hour at 37° C. The formula is thus :

Serum, 0.1 c.c.

Extract, 1 in 15.	0.5 c.c.	} 1 c.c.
Complement, $2\frac{1}{2}$ M.H.D., in D.	0.5 c.c.	

Incubate 1 hour at 37° C. in air.

Sensitized red cells, 0.5 c.c.

Incubate 20 minutes at 37° C. in a water-bath.

Allow to stand at room temperature for one hour for cells to settle.

Test similarly 0.05, 0.025, 0.012, and 0.006 c.c. serum, and control as described.

The results are read according to the amount of haemolysis in each tube, as shown by the appearance of the supernatant fluid. Complete haemolysis in any tube is represented by 0, complete inhibition by 4, and other grades of haemolysis by intermediate figures. Thus a strongly positive reaction, with complete inhibition in every tube except the control, would be represented by 44444 and a completely negative by 00000. The standard for a positive from a diagnostic point of view is 30000—that is, not more than 25 per cent. haemolysis in the first tube (containing 0.1 c.c. serum). Reactions represented by 20000 and 10000 are, however, considered significant from the point of view of treatment.

*Browning and Mackenzie.*⁴³ The complement is previously titrated alone and with the amounts of extract and serum respectively to be used in the test, and the dose of complement used is 5 M.H.D. plus that which is deviated by extract and serum respectively acting alone.

Formula :

Tested serum, 0.05 c.c.

Complement as stated.

Ox-liver extract, 0.1 c.c. made up to 0.6 c.c. with saline, the dilution being effected as described (see p. 268).

Incubate for one hour at 37° C. and add 1.0 c.c. of a 3 per cent. suspension of the deposit of washed ox-cells, sensitized with 5 M.H.D. haemolytic amboceptor.

The quantitative estimation of the strength of the reaction is determined by the number of M.H.D. complement deviated by the serum-extract combination. In other tubes, therefore, are incubated the amounts of serum and extract mentioned above, with larger and larger amounts of complement.

Browning, Cruickshank, and Mackenzie's lecithin and lecithin-cholesterin method. This depends on the fact that a syphilitic serum when incubated with lecithin and cholesterin (see Appendix) will deviate much more complement than when incubated with lecithin only. In each of a series of test-tubes arranged in two

rows is placed 0.6 c.c. of a 1 in 12 dilution of the tested serum. In each tube in the front row is placed 0.6 c.c. of a 1 in 6 dilution of a 0.75 per cent. solution of ox-liver lecithin, and into each of the back row the same quantity of a saturated solution of cholesterin in the 0.75 per cent. solution of lecithin. Into the first tube of each row is placed 3 M.H.D. complement, into the next of each row, 4 M.H.D., and into the succeeding pairs 5, 6, 7, 12, and so on, M.H.D. complement respectively. The mixtures are incubated for one hour at 37° C. and 1.0 c.c. sensitized ox-cells added. After incubation for a further hour the results are read. According to the authors of this test, if a serum deviates 2-3 M.H.D. complement more in the lecithin-cholesterin series than in the lecithin series it is probably syphilitic, while if 5 (or more) M.H.D. complement more are deviated it is practically conclusive of syphilis. It is claimed for this test that it is independent of variations in the deviability or haemolytic power of the complement used and no other serum need be used as control.

Sormani.⁴⁴ The cells in a 5 per cent. suspension are sensitized with 8 M.H.D. haemolytic amboceptor, kept for two hours at 37° C., and then spun. The supernatant fluid, containing haemolytic serum over that which is required to sensitize the cells fully, is removed and replaced with saline.

As a preliminary to the test the complement is titrated to ascertain its M.H.D. In addition to this, the largest quantity of extract used in the test is incubated with falling quantities of complement. Thus in separate tubes are placed one volume of 1 in 10, 20, 25, 30, 50, and 100 guinea-pig-serum complement, and to each tube is added 0.25 c.c. extract. After incubation for one hour at 37° C., two volumes of sensitized cells are added, and incubation allowed to continue for half an hour. The smallest quantity of complement which produces complete haemolysis in this series is used in the test proper.

The test is carried out in six tubes. In each is placed one volume of 1 in 5 serum and in the first five the quantity of complement as ascertained above. In the sixth tube is placed 1 M.H.D. of complement. In the first five tubes are placed falling quantities of extract (generally alcoholic extract of syphilitic liver) thus,

0.25, 0.19, 0.13, 0.07, 0.01 c.c. After an hour's incubation at 37° C., the sensitized cells are added, and the results read after another half hour. In this case the strength of the reaction is determined by the quantity of extract required to bring about deviation of the complement, the smaller the quantity of extract required, the stronger the reaction.

*Noguchi's*⁴⁵ test is designed partly to overcome the objection that human serum contains haemolytic amboceptor for sheep cells, which introduces a variable into the test, and partly for use by the practitioner in his consulting-room. The haemolytic system is a suspension of washed human cells sensitized with anti-human amboceptor. The tested serum is not heated unless it is unduly anti-complementary or any other than an extract containing only acetone insoluble lipoids is used. If a protein-containing extract such as an unpurified alcoholic extract is used, the serum is heated and used in four times the quantity. The blood cells are obtained from a patient, 1 c.c. being dropped into 9 c.c. solution of sodium citrate in saline. They are washed in the usual way by spinning in the centrifugal machine, and made up to 10 c.c. with saline so that the strength of cells in the suspension is now 10 per cent. of the original. This may be added as such in a quantity of 0.1 c.c. or diluted to 1 in 10 and 1 c.c. added, the procedure differing slightly according to which is chosen. The haemolytic amboceptor is prepared by injecting rabbits intraperitoneally with increasing quantities of thoroughly washed human red cells (5 c.c. to 20 c.c.) at intervals of five days, bleeding to death, and removing the serum. The serum is taken up with blotting-paper, Schleich and Schull's No. 597 being recommended for this purpose. The soaked paper is laid to dry on non-absorbent, unbleached muslin, and when dry, cut up into strips about 5 mm. broad. The amboceptor is titrated against 1 c.c. of the 1 per cent. suspension of cells with 0.1 c.c. of a 1 in 2.5 dilution of fresh guinea-pig-serum complement. A series of tubes containing these quantities of cells and complement is laid out, and into each is put a definite, varying length of amboceptor paper, 1 mm., 2 mm., 3 mm., and so on. After incubation at 37° C. for two hours, the tube is sought which

contains the shortest length of amboceptor paper, and in which lysis is complete. This length represents one unit, and two units are used in the test. The extract is prepared as described in the Appendix, and may be used as emulsion or dried on paper. Formerly Noguchi recommended the use of complement dried on paper, but would now restrict this to places, such as camps, where fresh guinea-pig serum could not be obtained. The formula for the test is thus :

Tested serum, if unheated, 1 drop (0.02 c.c.) ; if heated,
4 drops (0.08 c.c.).

Complement, 0.1 c.c. of a 1 in 2.5 dilution.

Amboceptor paper, length of two units.

Extract, either emulsion or paper slip, 0.1 c.c. of a 0.3 per cent. suspension of lipoids (see Appendix).

Salt solution, 0.9 c.c.

Incubate in a warm place, not hotter than 37° C., for an hour, or in a water-bath at 37° C. for twenty minutes, and add of 10 per cent. suspension of human cells, 0.1 c.c. Another procedure is to add to the mixture, before incubation, 1 c.c. of a 1 per cent. suspension of cells instead of the salt solution and amboceptor, and to add the amboceptor slip after the incubation.

It will be seen, from the few examples quoted, how much the practice of individual workers differs, not only from the original but from others, and it might almost be said there are as many methods of conducting this test as laboratories in which it is carried out. Probably each is reliable in that it gives positive reactions only with syphilitic sera, but in the case of weakly acting sera—such, for instance, as those of patients under observation after a course or courses of salvarsan treatment, and where the spirochaete is beginning to be active again—one method will doubtless still give negative reactions where others give positive. The latter will give earlier warning, in other words, that the patient is not yet cured, and the patient will have the advantage of treatment when the spirochaete has not made so much headway as if his serum were tested by a less delicate method. The necessity for a standard method of carrying out the test which is at once the most simple, delicate, and reliable must be apparent.

One of the most important questions in this connexion is the preparation of a standard extract, and the work of McIntosh and Fildes and Walker and Swift to this purpose constitutes a substantial advance. The best method of incubating and the reading of the results by more exact methods than by the eye, aided by experience, seem to be contained in the technique of Thomsen and Boas. Questions still to be decided are the optimum quantities of extract, serum, and complement respectively to be used in the test, and the best method of sensitizing the cells. It seems to the author that these questions could quickly be decided by a small party of workers with leisure and sufficient material on which to work.

CHAPTER XXIV

Modifications of the Wassermann Reaction. As mentioned, most workers employ a technique which is in some particular a modification of the original, but by this term we mean here those tests in which, chiefly for the sake of simplicity, the worker relies for the complement and amboceptor, or for the complement alone, on that which is contained in the tested serum. It will be possible here to mention only a few of the numerous modifications which have been devised on these principles. In all of them the serum must be quite fresh, preferably not more than 24–48 hours old ; otherwise its complement may be absent or defective.

*Modifications in which the Amboceptor is Artificial, as in the Original Test, but the Complement is contained in the Patient's Serum—Stern's Test.*⁴⁶ This test was designed to be used in conjunction with the original.

The original directions were to use the same amount of serum as for the original, but two quantities of extract, respectively two-fifths and one-fifth the amount which is suitable for the original test. The strength of the blood suspension is 2·5 per cent., and the cells are sensitized with 9–12 M.H.D. of haemolytic amboceptor. I have used rather smaller amounts of extract than those originally recommended, viz. one-third and one-sixth respectively the amount used in the original. I have tested a very large number of sera by this method, always in conjunction with the original, and found the following to be a convenient plan of carrying it out.

Each serum is tested in three tubes placed one behind the other. Into each of these is put one volume of a 1 in 5 dilution of the *unheated* serum. The extract is diluted with saline to make two strengths, respectively one-third and one-sixth of that used in the test by the original method. Into the front tube is put one volume of the extract in the stronger of the two dilutions. In the second is placed one volume of the weaker

extract, and in the back tube, a volume of saline to make the bulk equal in all. The tubes are placed in the incubator, and at the end of half an hour a volume of the 2·5 per cent. suspension of heavily sensitized cells is added to each. Normal and syphilitic control sera must be tested also. In reading the results, particular attention must be paid to the back row tubes containing no extract, and the test of any serum rejected when haemolysis is not absolutely complete in this tube. When no lysis occurs in either of the two extract tubes the reaction may

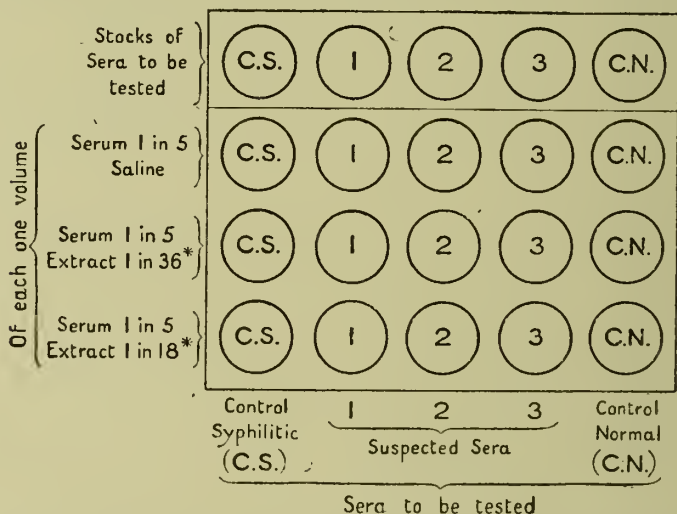


FIG. 6. Plan of arrangement of tubes for Stern's test. After preliminary incubation, to each tube is added one volume of a 2·5 per cent. suspension of sensitized cells.

* Strength of extract based here on assumption that 1 in 6 is suitable for the original test.

be considered as stronger than when the tube containing the smaller amount of extract shows haemolysis.

Emery⁴⁷ and Birt⁴⁸ have each devised modifications which rely on the complement in the unheated tested serum. In each of these modifications the haemolytic system is a suspension of human cells sensitized with rabbit's anti-human serum.

Emery's method is as follows: The extract is standardized against a normal serum by incubating four volumes of each of a number of varying dilutions, 1 in 10, 12½, 14, in salt solution, with one volume of non-syphilitic serum. The mixtures are incubated in a water-bath for five minutes at 37° C., and to each

is then added one volume of a 20 per cent. suspension of washed human cells which have been fully sensitized. The result is read in a few minutes, and that strength of extract is chosen which allows of almost complete lysis with the normal serum. In the test proper one volume of the tested serum is put up with four volumes of extract, diluted according to the titration, and incubated for five minutes. In another tube are placed a volume of the same serum and four volumes of saline. After incubation, one volume of the 20 per cent. suspension of fully sensitized cells is added, and, after shaking, incubation continued for a few minutes longer. A control normal and a syphilitic serum are included in the series.

Birt's test does not even require the use of a centrifugal machine. The patient's blood is drawn off into a Wright's capsule, allowed to clot, and the pipette is then introduced into the clot, or the bottom of the capsule, to take up sufficient loose red corpuscles to make with the serum already drawn off a 5 per cent. suspension. Of this suspension one volume is placed in each of a number of test-tubes (say four). In one (control) is then placed four volumes of saline, and in each of the others four volumes of extract (heart) in varying dilution, thus :

No. 1 tube (control) contains one volume of 5 per cent. cells in serum, and four volumes of saline.

No. 2 contains one volume of cell-serum suspension, and four volumes of 1 in 50 extract.

Nos. 3 and 4 contain each a volume of cell-serum suspension, and respectively four volumes of 1 in 100 and 1 in 200 extract.

After incubation for half an hour in an ordinary incubator at 37° C., or for five minutes in a water-bath at 38° C., the haemolytic amboceptor (5 M.H.D.) is added to each tube.

A normal and a syphilitic serum are included in the series, and, after addition of the amboceptor, incubation is allowed to proceed till the normal serum control shows complete haemolysis in all its tubes. The varying quantities of extract which are used are intended for the estimation of the strength of the reaction, the strongest being that where no haemolysis occurs in any of

tubes 2, 3, and 4, and the weakest that where there is haemolysis in tubes 3 and 4.

Of the modifications which rely for both complement and amboceptor on that which is contained in the patient's own serum, the best known is Hecht's,⁴⁹ which has been modified in a few technical details by Fleming.⁵⁰ The following is Fleming's method: The extract is made by grinding up heart muscle with absolute alcohol in the proportion of one of heart to five of alcohol. The mixture is heated at 60° C. for an hour, allowed to stand for twenty-four hours, and then decanted. The strength of the extract to use in the test is determined by incubating four volumes of each of a number of varying strengths of it (1½, 2½, 5, 10, &c., per cent.) in saline, with one volume of a normal and a syphilitic serum respectively. The mixtures are incubated for an hour at 37° C., and to each tube is then added one volume of a 10 per cent. suspension of washed sheep cells. That strength of extract is chosen which allows complete haemolysis with a normal serum. In the test one volume of the tested serum is placed in each of two tubes. In one of these is placed four volumes of the diluted extract, and in the other (control) four volumes of saline. After incubation for one hour at 37° C., to each tube is added one volume of the 10 per cent. suspension of sheep cells. If the control tube of any test shows defective lysis, it may be due to lack of natural amboceptor in the tested serum. In this case Fleming recommends the addition of a volume of heated normal serum. If lysis is still defective, the complement must be deficient and the test must be repeated, with the addition of a volume of normal serum to supply the complement.

Criticism of the Modifications. In a strictly scientific test of a number of sera for the presence in them of a substance or quality which varies in amount, and when the decision rests on the presence of an excess or a normal amount of that substance, as in testing for the Wassermann substance, it is necessary that all the reagents for the test should respectively be derived from the same source, be in the same amount, and be treated in the same way. This principle is, as far as possible, carried

out in the original Wassermann test. The amboceptor for all the tests comes from the same source, and is used in the same amounts throughout. Similarly with the complement. With the modifications described above it is different. In the Stern, Emery, and Birt tests the complement, though fairly constant, is an unknown quantity unless the worker takes the trouble to titrate out this substance in each separate serum; in any case it is possible that the amount in any tested serum may be widely different from that in the controls with which the result is compared; or it might be more sensitive to deviation, as Browning and Mackenzie maintain is the case with some samples of guinea-pig-serum complement, though we have no means of ascertaining this. In the Hecht technique a still further variable is added, since the haemolytic amboceptor also is derived from the tested serum. About 10 per cent. of human sera contain no haemolytic amboceptor for sheep's cells.

If there is no lysis in a tube containing extract and serum, while the control, containing serum only, is completely haemolysed, this is recorded as positive. But if a normal serum contained a diminished amount of complement it might show complete lysis in the control tube and none in the extract tube, since it must be remembered that extract in the presence of a normal serum will deviate complement, particularly when the serum is unheated, as in the case of the modifications. I have frequently seen this happen in the Stern test. A serum tested on one day gave a negative reaction, and on the next, or the day after that, a positive with a perfectly clean control. Though the complement titre of perfectly fresh human sera may not vary very greatly, its stability does so considerably. Out of 1,824 specimens, taken for the most part on the day before the test at Rochester Row, 360 were found to be deficient in complement, while exceptionally sera which have travelled from Egypt have given negative reactions. Most advocates of these modifications stipulate for serum 24-48 hours old. It is a question in the case of the above-mentioned 1,824 sera, none of which were more than 48 hours old, if 360 were too defective in complement to show a clean control, how many more had

only just enough complement to clear the control. As a matter of fact, a small percentage (about four) of normal sera have given positive reactions to the Stern test in my hands, though I use a smaller proportion of extract than that originally recommended, and am not satisfied with less than rapid and perfect haemolysis in the control.

A practical disadvantage of relying exclusively on one of these modifications is that many sera sent by post arrive with the natural complement so defective that the test fails. Out of 1,064 sera received in 1913, from stations in the United Kingdom, and tested at Rochester Row, the test failed in 438 on this account. It is true that one can, as Fleming recommends, re-test with the addition of a normal serum, but this amounts to a bad method of carrying out the original test.

Even on the score of simplicity, there is no justification for the Hecht test, since anti-sheep serum can be purchased if the worker is not in a position to make it for himself.

The advantage of the modifications lies in their greater delicacy, which probably depends mainly on the fact that the tested serum is not heated. For this reason it is useful to test each serum by a modification as well as by the original. In early cases where for some reason the spirochaete has not been found, and the patient is under observation, the modification may give warning to test again at an earlier date than would otherwise be done in routine practice; this applies also to the observation of patients who have received what is believed to be an adequate amount of treatment. After suspending treatment, if the patient is uncured, the serum may react still earlier to the modification than to the original test, and I think that under these circumstances a positive reaction is sufficient justification to recommence treatment without waiting for a reaction to the original test.

Briefly, a diagnosis of syphilis is a serious matter, and should be based on an absolutely reliable test, the original; over-treatment of a patient is an error on the right side, and is justified by a positive reaction to a test which may give positive reactions in a small percentage of non-syphilitic cases.

CHAPTER XXV

The Nature of the Wassermann Reaction and its Occurrence in other Diseases. The nature of the substance in syphilitic serum which interacts with organ extract to bind complement is still in dispute. That it is not specific antibody to the *Spirochaete pallida* in those cases where an alcoholic extract of normal organ is used as 'antigen' must be conceded even by those who maintain that antibody is concerned in the reaction when watery extract of syphilitic liver is used. But watery extract of syphilitic liver contains other substances besides extract of *pallida*. A syphilitic liver is one in which profound bio-chemical changes have occurred, releasing, possibly, those substances necessary to the reaction which can only be obtained from normal organ by preliminary treatment with alcohol. Bruck⁵¹ found that if normal organ were treated with a 1 in 5,000 solution of caustic potash the result was an extract which worked as well as a watery extract of syphilitic liver. Noguchi⁵² found that the serum of rabbits which had been immunized by injections of dead *pallida* culture bound complement with *pallida* culture as antigen, but not when his antigen composed of pure lipoids was used. On the other hand, rabbits which had been infected with syphilis did not bind complement with *pallida* antigen, but did so with lipoid antigen. Further, using *pallida* antigen for the testing of human syphilitic serum, he found that as a rule the serum of early cases did not react while that of later cases and those which had been treated with salvarsan reacted better. He believes, therefore, that in the serum of syphilitics we may detect two substances by the complement deviation test; one is most in evidence in the early stages, and binds complement when in contact with lipoids such as are contained in an alcoholic extract of normal organ, or in a purer form in the acetone

insoluble fraction of such an extract, and the other, antibody to pallida, which is not greatly in evidence at any time in syphilis, and is particularly scarce in the early stages. On this theory, watery extract of syphilitic liver acts by virtue of its content in lipoids, in the early stage at any rate, and not because of its content in pallida substance. It would serve no useful purpose to enter into a long technical discussion of the nature of this substance, and the views of only one or two other workers will be mentioned here. Citron⁵³ holds that in syphilis a toxo-lipoid is formed in the tissues which gives rise to the production of an anti-toxo-lipoid in the serum; this reacts with the lipoids in the extract to bind complement. Bruck and Stern⁵⁴ believe that a proteo-lipoid passes into the serum, which binds complement in combination with nearly related substance in the extract. Elias, Neubauer, Porges, and Salomon⁵⁵ believe that the substance is a changed albumin, and the reaction of the nature of a precipitin one, the precipitin absorbing the complement. This view is held also by Levaditi and Yamanouchi and Jacobsthal. The last named has based a test for syphilis on the precipitation which occurs when syphilitic serum and organ extract are incubated together (see p. 304). Whatever its actual chemical nature may be, the majority of workers believe it to be a degeneration product of the tissues. It appears as a result of the action of the parasite, and is therefore most in evidence when the spirochaete is most active, if we may judge from clinical signs and the effect of treatment on the reaction.

Wassermann Reaction in other Diseases. It would naturally be thought that, as the Wassermann substance is not a true antibody, it should be found in the serum of patients suffering from other diseases. This has proved to be true, but not to an extent which detracts from the clinical value of the test.

The blood-serum of patients suffering from the following diseases has been found by various observers to give the Wassermann reaction: Yaws, leprosy (chiefly the tubercous variety), trypanosomiasis, relapsing fever, malaria, scarlet fever, tropical ulcer, pellagra, beri-beri, pneumonia, late tuberculosis, diabetes mellitus, typhoid fever, and malignant tumours. A positive

reaction has occasionally been given by the serum of patients *in articulo mortis*, and quite a large percentage of the sera of corpses give a Wassermann reaction. In a few cases the blood-serum of patients under general anæsthesia has given a positive reaction, and a transitory Wassermann reaction has occasionally been given by patients in eclampsia.

None of these are conditions which are likely to be confused with syphilis, and a few remarks only are necessary regarding them. Yaws and relapsing fever are diseases due to spirochaetes, and the *Spirochaete pertenuis* of yaws can be distinguished from *Spirochaete pallida* only by animal experiments. In malaria the reaction has only occasionally been given, and then only at the height of the fever. Scarlet fever patients were found by Much and Eichelberg⁵⁶ to give the reaction in 40 per cent. of their cases, but this proportion has been found by other observers to be much too high. Counting Much and Eichelberg's first 25 cases, McIntosh and Fildes⁵⁷ have collected the records of 538 tests by various workers, and the total number of positive reactions amounted only to 28, or 5·2 per cent. The reaction quickly disappears in convalescence. From the work of Bruck and Cohn⁵⁸ it would appear that some extracts give a high proportion of positive reactions in scarlet fever, and others none, both varieties being equally good for deviating complement with syphilitic serum. In tropical ulcer Schüffner⁵⁹ found that out of 106 cases 86 per cent. gave the reaction, but only with watery extract; when alcoholic extract was used only 3 per cent. gave a positive reaction.

The reactions given by the serum of patients suffering from late tuberculosis and carcinoma are quite possibly associated with the great tissue destruction which accompanies these diseases. With regard to typhoid, pneumonia, and diabetes, the instances in which a positive reaction has been found are relatively very scarce, and it is possible, as indeed some of the observers who have recorded these results have admitted in later papers, that in most of these the technique was at fault.

CHAPTER XXVI

The Wassermann Reaction in Syphilis. Primary Stage. It is impossible to give statistics which will convey any idea of the percentage of positive reactions to be expected in this stage. Everything depends on the age of the sore; when this first appears the reaction is almost always negative; when the sore is fifteen days old the majority, and just before the outbreak of the secondary symptoms almost all cases give a positive reaction, provided they have received no treatment. The writer's experience is that when the sore has become indurated a positive reaction may be expected in untreated cases.

It is in the early secondary stage of untreated syphilis that the highest percentage of positive reactions is obtained; Bruck⁶⁰ gives 90 per cent., rather a low figure; McIntosh and Fildes state their belief that 100 per cent. are positive. I have tested 339 cases in this stage which were either entirely untreated or had received less than six mercurial injections, and obtained 96.4 per cent. of positive reactions to the original test; while out of 124 cases tested by Stern's modification, 121 were positive. It is possible that if all the sera had been tested with the heart-cholesterin extract at present in use, a higher percentage of positive reactions would have occurred. Treatment causes an appreciable falling off in the number of positive reactions, and it is quite possible that some of the cases I have classed as untreated had really been taking 'blood mixture' before admission. Secret treatment, however, does not account for all the negative reactions I have obtained in untreated secondary cases. Having repeatedly tested the blood-serum of many soldiers, I have records of a few cases which seemed naturally refractory in their response to the Wassermann test, and even to Stern's modification. On first admission with well-marked secondary signs, and subsequently when relapses occurred months after any

treatment had been given, the reaction was negative, and one can only conclude that it was a peculiarity of these patients that they gave a negative when a positive would be expected. Craig and Nichols⁶¹ hold that the ingestion of alcohol temporarily renders the reaction negative. If this were so to the extent which these workers maintain is the case, the proportion of positive reactions given by soldiers should be very low.

In later stages of syphilis, with some exceptions mentioned later, the proportion of positive reactions is considerably affected by treatment, and, generally speaking, it varies inversely with the efficiency of such treatment. In compiling Table I, which shows the results obtained by different workers at various stages of syphilis and in parasyphilis, I have endeavoured to separate untreated from all cases, and the higher percentage of positive reactions given by untreated cases will be seen. The factor introduced by treatment must be taken into account, therefore, in gauging the likelihood of a positive reaction in these stages.

In tertiary syphilis the statistics collected by McIntosh and Fildes show 83 per cent. positive out of 1,043 cases, their own cases showing 95 per cent. positive.

In the latent stages it is particularly hard to separate the influence of treatment from that of other factors. The most reliable results relate to the mothers of congenital syphilitics who denied knowledge of any infection, since one may suppose that these were untreated. From the carefully collected statistics of McIntosh and Fildes, out of 196 such cases 143 gave a positive reaction. This corresponds very closely with the 75 per cent. of positives which Boas obtained in latent cases which were either badly treated or untreated.

In congenital syphilis with manifest signs almost all cases are positive. In latent congenital syphilitics about 60 per cent. give the reaction.

The examination of the serum of congenitally syphilitic children and of their parents, and that of children suffering from congenital defects, has thrown light on several questions of practical interest.

Thomsen and Boas⁶⁶ examined the serum of 88 infants,

either born of syphilitic mothers or themselves showing signs of syphilis, and of the children 31 gave a positive reaction. In 4 of these the reaction disappeared, and in a period which ranged from 3 to 9 months none showed any further symptoms. The explanation is that the Wassermann substance, without the virus, passed from the mother to the child, and the latter excreted it just as it would any other foreign proteid. All of the 27 remaining infants which gave a positive reaction suffered from manifest syphilis either at the time or within three months.

Of the 57 which gave a negative reaction, 42 remained apparently healthy over a period of several months, and 13 developed symptoms with a positive reaction. The remaining 2 died before the appearance of symptoms, but the organs showed syphilitic changes. Probably, as Boas remarks, if all these children had been examined by the more refined technique of the present day, a number of these 15 originally negatively reacting sera would have given positive reactions.

Examination of the umbilical cord of each of these 88 infants for histological changes showed that this may be diseased but the Wassermann reaction negative, and vice versa. Probably, however, histological changes indicate that syphilis will manifest itself sooner or later.

The conclusion from these observations is that a positive reaction in the infant's serum at birth indicates a strong probability of syphilis in the child. This would amount to a certainty if the serum of the mother gave a negative reaction. A negative reaction, especially with the modern technique, is good, but not certain, evidence that the child has not been infected.

Examination of the serum of 46 mothers of infants which remained free from signs for three months, showed 17 positive and 29 negative. Out of 81 mothers of syphilitic infants, 61 gave a positive reaction, and 11 of these had no knowledge of infection. One of the mothers of the syphilitic infants had been infected 20 years previously, and had meantime given birth to several healthy children.

It will be seen from this that a positive reaction in the mother is unfavourable to the child's chances of escaping infection,

while a negative is favourable. Neither, however, gives a certain prognosis.

The high percentage of mothers of syphilitic infants who give a positive Wassermann reaction, and the large proportion of these who have no knowledge of having ever suffered from syphilis, indicates that mothers are not infected by suckling their syphilitic infants (Colles' law), because they are already suffering from the disease.

In latent cases of congenital syphilis the reaction appears to die out in a large proportion of cases after 14 years of age. Regarding the relation of congenital syphilis to mental deficiency, particularly to idiocy, the Wassermann test appears likely to show that syphilis is a larger factor than was believed. The clinical evidence generally goes to show that an almost negligible proportion of imbeciles show evidence of syphilis. It is well known, however, that in acquired syphilis the gravest lesions of the central nervous system, tabes and general paralysis, are commonly associated with histories of little or no later clinical evidence of syphilis beyond the primary sore. Clinical evidence counts for very little, therefore, against the connexion between syphilis and imbecility. Dean⁶⁷ examined the blood-serum of 330 idiots, inmates of the Wilhelmstift, Potsdam, and in 287 cases of simple idiocy found 44 positive; in 15 of congenital spastic diplegia, 1 was positive; in 14 of hydrocephalus, 4 were positive; in 7 deaf mutes, 1 was positive; 1 epileptic was positive, and 1 mongol and 1 case of progressive muscular dystrophy were both negative; altogether, 51 positive out of 330 cases, or 15.4 per cent. Only 9 of the 330 cases showed clinical signs of syphilis, and 2 of these gave a negative reaction. Grouped by ages, 21.2 per cent. of 94 patients under 10 were positive; 16.9 per cent. of 142, aged 11 to 15 years; and 6 per cent. of 66, aged 16 to 20 years—showing, as Dean has remarked, that the reaction tends to die out after 14 years of age. Raviart, Breton, Petit, Gayet, and Cannee⁶⁸ found 30 per cent. of 246 idiots positive. Atwood⁶⁹ found 14 per cent. of 204 cases positive. Chislett⁷⁰ found 8 out of 14 idiots positive, and Krober⁷¹ 21.4 per cent. of 262 idiots. Fraser and Watson⁷² examined 204 cases of mental

deficiency, and found 51 per cent. of 94 cases of simple mental defect positive, 45 per cent. of 33 similar cases with epilepsy, 41 per cent. of 67 cases of mental and physical defect, and 40 per cent. of 10 cases with epilepsy only. The high percentage of positive reactions found by these workers is probably due, as Browning says, to the fact that these cases were all very young. It appears, therefore, that, although Boas⁷³ reports only 31 positive out of 2,061 cases of mental defect, there is a much closer connexion between syphilis and congenital mental defects than was believed.

With regard to other children's diseases, Browning⁷⁴ has collected some interesting facts from which the following are quoted. Out of 25 cases of heart disease in children, Watson found that 17 gave a positive and 1 a doubtful reaction. Out of 46 cases of congenital deafness, Browning and Cruickshank, in conjunction with Love,⁷⁵ found 6 positive; out of 36 cases of acquired deafness, 7 were positive, and 4 cases of acquired deafness with interstitial keratitis were all positive.

In so-called parasymphilis the test is applied to the cerebro-spinal fluid as well as to the blood-serum, and the character of the reaction obtained in each of these has an important diagnostic significance, which will be discussed later when dealing with the examination of the cerebro-spinal fluid.

In tabes the reaction given by the blood-serum is influenced again by the amount of previous treatment. Thus, Boas found that 100 per cent. of untreated tabetics gave the reaction, but only about 42 per cent. of treated cases.

In general paralysis, Browning and Mackenzie⁷⁶ obtained a positive reaction in 96 per cent. of their cases. Plaut's⁷⁷ cases gave 99 per cent. positive, and Boas obtained 100 per cent. positive in 243 cases. Probably the most valuable work in this connexion is that of Candler and Mann,⁷⁸ who give the statistics relating to 109 cases tested by them in conjunction with Henderson Smith, where the diagnosis was confirmed by autopsy. Altogether a positive reaction was obtained at some time in 107, or 98.1 per cent. In five of these the reaction was at first negative, and subsequently found to be positive. This illustrates the importance of repeating the test in suspected cases.

The Effect of Treatment on the Wassermann Reaction. This has been mentioned in explanation of the varying results obtained by different workers, especially in the later stages of syphilis. It is not easy to obtain from the literature particulars which give a reliable idea of the influence of treatment on the Wassermann reaction. With civilians it is difficult to be certain that the patients really take the treatment prescribed, especially if this is in the form of mercury by the mouth or inunctions, unless the latter are applied by a skilled and conscientious rubber. A great deal also depends on the age of the infection and the amount of previous treatment. In old-standing cases where treatment has been only symptomatic the reaction is particularly difficult, and sometimes impossible, to convert to negative. The same applies to congenital cases, and unless the author gives full particulars regarding these factors it is impossible to distinguish their influence from that of the treatment.

On this account I venture to show in Tables II and III only the results obtained at Rochester Row with the serum of soldiers who were treated regularly from an early stage of the disease. In Table III the difficulty of converting an old-standing positive Wassermann reaction to negative is partly illustrated by the results obtained with cases which had been previously treated, but in which mercurial treatment had failed to prevent frequent relapses.

When the test is carried out in a quantitative manner the influence of treatment is quickly seen, the reaction becoming weaker in the majority of cases by the end of the first course of intramuscular injections, and during the two years of regular treatment by intramuscular injections it is the exception to find cases reacting so strongly positive as untreated cases.

It is rather difficult to explain why it is that in congenital syphilitics, in old-standing neglected cases and in general paralysis, treatment should have so little or no influence on the reaction. The usual explanation is that the spirochaetes have become so deeply imbedded in the tissues that it is impossible to damage them, but it is possible that in response to the long-continued action of the spirochaetes the tissues have developed the habit

TABLE II

SHOWING THE EFFECT OF MERCURIAL INJECTIONS * ON THE WASSERMANN REACTION

<i>Tested after</i>	<i>Total Cases.</i>	<i>Positive.</i>	<i>Per cent. Positive.</i>
1st course of 6-9 weekly injections	95	69	72.6
1st interval of 6-8 weeks	23	16	69.5
2nd course of 4-6 fortnightly injections . . .	82	43	52.4
2nd interval of 2-3 months	29	20	68.9
3rd course of 4 fortnightly injections	83	44	53.0
3rd interval of 3 months	36	20	55.5
4th course of 4 fortnightly injections	130	45	34.6
4th interval of 4-6 months	43	24	55.8
5th course of 4 fortnightly injections	67	24	35.8
5th interval of 1 month	62	16	25.8
6th or 7th course of 4 fortnightly injections .	115	43	37.3
Three months after two years' regular treatment with mercurial injections	492	224	45.5

* Mercurial cream (Hg gr. 1 in each), mercury salicylate (gr. $1\frac{1}{2}$ in each), or calomel cream (Hg_2Cl_2 gr. $\frac{3}{4}$ in each).

TABLE III

SHOWING THE IMMEDIATE EFFECT OF SALVARSAN, ALONE OR IN CONJUNCTION WITH MERCURIAL INJECTIONS, ON THE WASSERMANN REACTION (tests not less than two nor more than six months after first injection of salvarsan).

		<i>Total Cases.</i>	<i>Previously Positive.</i>	<i>Remained Positive.</i>	<i>Per cent. remained Positive.</i>	<i>Previously Negative.</i>	<i>Became Positive.</i>	<i>Per cent. became Positive.</i>	<i>Total remained or became Positive.</i>	<i>Per cent. remained or became Positive.</i>
Previously untreated (primary and secondary) cases	Salvarsan in conjunction with mercurial injections	154	101	10	9·9	53	3	5·6	13	8·4
	All cases	257	178	21	11·7	79	7	8·8	28	10·8
Previously treated; chiefly relapses under mercurial treatment	All cases	191	148	47	31·7	43	5	11·6	52	27·2
	Totals of all cases	448	326	68	20·8	122	12	9·8	80	17·8

of forming Wassermann substances, and continue it long after the micro-organisms have been destroyed. Certainly in a proportion of these stubborn cases the reaction becomes weaker

under efficient treatment, but there are many others on whose Wassermann reaction the most strenuous treatment with salvarsan and mercury has not had the slightest effect, and the future of these patients will be interesting. In the present state of our knowledge, whatever we may hope is the true explanation, it is safer to assume that syphilitics who give a persistently positive reaction are uncured, and to act accordingly.

The Wassermann Reaction in Diagnosis and Treatment. In *Diagnosis.* The significance of a positive reaction will be gathered from the above remarks. Excluding a few conditions which have been discussed and can easily be excluded by other methods of diagnosis, a positive Wassermann reaction to the original test indicates the presence of syphilis.

It is necessary here to caution against the tendency to make the presence of syphilis exclude that of other diseases. A positive Wassermann reaction which happens to coincide with a hammer-toe does not imply that the hammer-toe is due to syphilis; nor does a positive Wassermann exclude epithelioma of the tongue, possibly engrafted on leukoplakia.

Regarding the significance of a negative reaction, it must at once be said that there is no stage of syphilis in which the percentage of positive reactions is 100, so that a negative reaction can never absolutely exclude syphilis, even in untreated cases, while if anti-syphilitic treatment has recently been administered, a negative reaction is of no value whatever. At the same time, in certain stages the evidence afforded by a negative reaction is very weighty. In cases where the diagnosis rests between early secondary syphilis and some other disease, in the absence of specific treatment a negative reaction, especially if repeated once or twice, would be almost conclusive against syphilis. In later stages the value of a negative reaction is not so great, though all the evidence points to the fact that in untreated cases a very high percentage of positive reactions is to be expected here. A negative reaction with the serum and, as will be seen later, with the cerebro-spinal fluid in cases of disturbance of the cerebral nervous system, is very strong evidence against general paralysis.

In Treatment. The value of the Wassermann test in estimating the effect of treatment in syphilis is very generally recognized. The effect of mercury and salvarsan treatments respectively on the reaction is illustrated in Tables II and III. The difference between mercury and salvarsan as regards their effect in converting the reaction to negative coincides very closely with other facts, clinical and microscopical, which attest the more profound influence of salvarsan on syphilis, and shows that the Wassermann test is a reliable guide in estimating the relative values of different lines of anti-syphilitic treatment.

If the test is conducted in a quantitative manner so as to estimate the strength of the reaction it gives very early information as to the chances of the treatment proving successful. Taking, for example, the case of a patient giving a strongly positive reaction and treated with salvarsan, if the reaction is going to become negative it will have changed from the original + + + to + + or + in two weeks; at the end of three to four weeks it is \pm or $\underline{\pm}$, and in five to six weeks it is completely negative to the original test. If at the end of three weeks it is still + + + one may expect that it will remain positive unless further treatment is administered.

In the majority of cases where the reaction previously positive has been converted to negative, but the disease is really uncured, the Wassermann reaction becomes positive before the clinical signs reappear, so that the test generally gives warning earlier than clinical signs that the disease is not yet cured.

In deciding the question whether a patient is cured and treatment may be stopped entirely, the Wassermann reaction is useful, but great caution must be exercised when a negative result is obtained. Assuming that the patient is not cured, the more recently treatment has been administered the more likely is the reaction to be negative, and vice versa, so that a negative reaction a year after suspension of all treatment is of considerably more value than one only three months after. It is generally said that a series of three negative reactions at three-monthly intervals, commencing three months after suspending treatment, may be accepted as evidence of cure. In addition to this I always

advise patients to have a test once every six or twelve months afterwards for some years. The trouble to the patient is, after all, trifling, and the test has not been long enough in use to enable us to fix an absolute standard of cure ; it is well therefore to keep on the safe side.

A negative reaction may have its value enhanced by administering a provocative dose of salvarsan (0.2-0.3 grm.) and then testing the blood after two, six, and thirteen days. The assumption is that if spirochaetes are still present the dose of salvarsan will stir them up temporarily to renewed activity, which will be reflected in a positive Wassermann reaction. In a few cases I have seen the reaction converted to positive in this way, and have certainly not seen a patient who gave a negative reaction after a provocative injection of salvarsan give a positive reaction later. Our experience is too limited, however, to judge this question absolutely.

CHAPTER XXVII

Other Serum Tests for Syphilis. Many other tests have been evolved, chiefly with the object of dispensing with the services of the trained pathologist, but with indifferent success. Some of them, e.g. the epiphanin reaction, appear more complicated than the Wassermann test; others, like the precipitation of syphilitic serum with distilled water (Klausner⁷⁹) or precipitation of a syphilitic serum on the addition of glycocholate of soda (Elias, Neubauer, Porges, and Salomon⁸⁰) and the colour reaction of Schurmann,⁸¹ are not specific to syphilis.

A test which may be found useful under special circumstances is the Herman-Perutz reaction. According to Jensen and Feilberg,⁸² though it does not give such a high percentage of positives as the Wassermann test, it never gives a positive with a negative-to-Wassermann serum, so that it may be used as a preliminary, resorting to the Wassermann test only when the H.-P. reaction is negative. The test, as modified by Jensen and Feilberg, is carried out as follows:

Two solutions are prepared—

A. Sodium glycocholate	2.0
Cholesterin	0.4
Alcohol, 95 per cent.	100.0

This may be kept as a stock solution.

B. A freshly prepared 2 per cent. solution of glycocholate of soda solution in distilled water.

Equal parts of solution *B* and a 1 in 20 dilution of solution *A* in distilled water are mixed together, and of the mixture 0.4 c.c. is added to an equal quantity of the serum to be tested in a test-tube. The serum is inactivated by heat beforehand. The tube is then shaken and kept at 22° C. till the following day. A flocculent precipitate indicates a positive reaction.

My limited experience with this test confirms the opinion of Jensen and Feilberg. One hundred and thirty-five sera were

tested, and 19 gave a positive reaction. All of these but one were positive to the Wassermann test, and this patient was syphilitic. Of the 116 sera which were negative to the H.-P. test, 15 were positive to the Wassermann and 101 were negative. Six of the sera which gave a positive H.-P. reaction were from clinically latent syphilitics.

The tubes were kept at room temperature and the sera were tested both heated and unheated. No normal unheated serum gave a positive reaction, but, on the whole, the unheated syphilitic sera gave stronger reactions.

Thomsen and Boas⁸³ have tested this method on 323 cases, of which 241 were syphilitic and gave 62 per cent. positive reactions to the Wassermann test and 43 per cent. to the Herman-Perutz. Of the 182 non-syphilitic cases, 3 per cent. gave a positive reaction to the Herman-Perutz test. They believe that this test is the best of the precipitation methods but not so good as the Wassermann. They recommend careful selection of the strength of sodium glycocholate solution. The best method is to test the strength of the solution by counting the drops to a given volume against those to a similar volume of distilled water; the best results are obtained when the proportion is 55 to 58, which is given by a 2 per cent. solution of Merck's purissimus sodium glycocholate.

Möller⁸⁴ also recommends that only the purest sodium glycocholate be used in this test.

Hammeltoft⁸⁵ in 156 cases found as many positive to this test as to the Wassermann, but practically all others agree that it is not so delicate.

Another precipitation test is that of Jacobsthal.⁸⁶ The serum is diluted and mixed with alcoholic extract of syphilitic infant's liver. After incubation at 37° C. for 30 minutes some of the mixture is examined by dark-ground illumination, when, in place of the bluish appearance, with fine, evenly distributed granules, which characterized the mixture before incubation, irregular flakes and lumps are seen. Bruck⁸⁷ has tested this method and concludes that it is not clinically useful, though interesting with regard to theories on the nature of the Wassermann reaction.

Weil considers that increased resistance of the blood-cells to lysis by cobra venene is specific to syphilis and that this property affords a useful test when the Wassermann test is doubtful. Stone⁸⁸ found that a 4 per cent. suspension of normal human cells was haemolysed by cobra venene when the latter was present in the proportion of 1 in 70,000 to 1 in 80,000. The cells of syphilitic blood, on the other hand, did not dissolve till the proportion of venene was raised to 1 in 15,000 to 1 in 40,000. In 112 cases of syphilis he got 87·8 per cent. positive in the secondary and 83·4 per cent. in the tertiary. In 88 controls there was one positive, a patient with a transitory morbilliform rash.

Kuschakoff⁸⁹ considers the test is not specific to syphilis, and it certainly requires confirmation.

*Karvo's conglutination reaction.*⁹⁰ This is really a modification of the Wassermann reaction and is based on Streng's⁹¹ observations on the properties of conglutinin. Briefly, this is a substance found in ox serum which has the property of causing certain bacteria and blood cells to run together into large clumps when they are also acted on by their specific antibodies and complement. Its action may be described as an exaggerated agglutination though it is not agglutinin. Since complement is necessary to its action, it is, like sensitized cells, an indicator of the presence or absence of this substance. The test is carried out as follows: A series of test-tubes is set out and into each is put 0·1 c.c. fresh horse serum (containing complement and also haemolytic amboceptor for guinea-pig's red cells) and 0·9 c.c. saline. Into every second tube is put 0·03 c.c. (two small capillary drops) of alcoholic extract of ox-heart. After shaking, two drops (0·05 c.c.) of the serum to be tested are put into each of a pair of tubes, the serum having previously been inactivated. The mixtures are shaken and left for 1½–2 hours at room temperature, and to each tube is then added 0·07 c.c. of a 25 per cent. suspension of guinea-pig's red cells. After shaking, the tubes are left for 15 minutes longer and to each is then added 0·03 c.c. of inactivated ox serum (containing conglutinin). The tubes are then moved to and fro, and in those tubes where the complement has

not been bound the evenly turbid mixture gradually begins to separate out into lumps which increase in size till a large coagulum forms. In the tubes containing positively reacting sera the mixture remains evenly turbid, since the complement necessary to the action of the conglutinin has been bound. Karvo's results were as follows. Out of 350 sera, the Wassermann and this reaction agreed in 278. In 66 the Wassermann reaction was negative and the Karvo positive; in 6 the Wassermann was positive and the Karvo negative. Other observers, including Hecht, Szabo and Wassermann, and Boas and Leschly, find that the reaction is often more difficult to read than when sensitized cells are used as the indicator.

Weichardt's ⁹²⁻⁷ epiphanin and Ascoli's ⁹⁸⁻¹⁰⁰ meiotagmine reactions were both originally designed to demonstrate the change in surface-tension which occurs when an antigen and its antibody are mixed. The technique in each case is too complicated to allow of a practical description in the space available, and only the principles will be given.

Weichardt, after testing other methods of indicating the change which occurs when antibody and antigen are mixed, found that the best indicator was the increased amount of barium hydroxide required to neutralize a given quantity of normal sulphuric acid.

Sciffert ¹⁰¹ has modified Weichardt's original technique so as to simplify it considerably. He considers it a reliable test. A solution of barium hydroxide is prepared of such a strength that 1 c.c. of it exactly neutralizes 1 c.c. of decinormal sulphuric acid. In a thoroughly clean test-glass are put 0.1 c.c. of a 1 in 10 dilution of the inactivated serum as fresh as possible and 0.1 c.c. of a 1 in 10 dilution of alcoholic extract of syphilitic infant's liver, the dilutions being made with saline. Then 1 c.c. of decinormal sulphuric acid is slowly added and a drop of phenolphthalein solution. To the mixture is then added 1 c.c. of the baryta solution prepared as described, and the test-glass is closed with a perfectly clean rubber bung. On shaking, a positive reaction is indicated by reddening of the mixture.

In 75 cases of syphilis tested by this method 64 agreed with

the Wassermann test ; of the remainder, 9 were positive to this test while all 11 were negative to the Wassermann test.

Ascoli relies in his meiostagmine reaction on the increase in the number of drops of a given amount of mixed antigen and antibody delivered by a Traube's¹⁰² stalagmometer¹⁰³ after incubation for 2 hours at 37° C. The test as applied by Izar and Uselli to the diagnosis of syphilis is briefly as follows. The antigen is an alcoholic extract of syphilitic infant's liver, concentrated at 47°-48° C. till a deposit begins to form and filtered. An extract of normal organ was also found to act when properly concentrated. The amount to be used is 1 c.c. of the smallest dilution which, after two hours' incubation with 9 c.c. of a 1 in 20 dilution of normal serum, will not give an increase of more than one in a drop-count of about 60. Having found the correct dilution of extract, 9 c.c. of a 1 in 20 dilution of the serum is mixed with 1 c.c. of the diluted extract and a count of the drops delivered by the stalagmometer taken at once. The mixture is then incubated at 37° C. for 2 hours and another count taken. If the number of drops has increased by two or more the reaction is considered positive.

Izar and Uselli's results showed that in 90 cases of syphilis 67 were positive and agreed with the Wassermann reaction, 9 gave a negative meiostagmine but a positive Wassermann ; 3 gave a doubtful meiostagmine but positive Wassermann ; 7 gave a positive meiostagmine but negative Wassermann, and 4 were negative to both tests ; but of 104 control cases, one gave a doubtful, and one a positive meiostagmine reaction. This was a case of erythema nodosum.

CHAPTER XXVIII

The Cerebro-Spinal Fluid in Syphilis and so-called Parasyphilis.

Until quite recently the interest in this subject was confined almost entirely to the investigation of the cerebro-spinal fluid in obvious disease of the central nervous system. Lately, however, the controversy over the causation of cranial nerve disturbances which have followed injections of salvarsan has stimulated a more extended research, and it has been found that a large proportion of patients suffering from late primary and early secondary syphilis show pathological changes of the cerebro-spinal fluid.

A very large proportion of these cases display no clinical symptoms to indicate any change in the central nervous system, or at most this is confined to a headache of greater or less severity. They are nevertheless candidates for subsequent lesions of the central nervous system, and it is often important from the point of view of treatment previously to examine their cerebro-spinal fluid.

Lumbar Puncture. This is best performed with the patient sitting on a stool with his head down between his knees and his lumbar region thrust well out. If done in bed the patient should lie on his left side with his right shoulder well over and his lumbar region arched out as much as possible. A line joining the highest points of the iliac crests crosses the spine of the fourth lumbar vertebra. Slightly below and to the right of this is the site of election for the puncture.

A needle four inches long and provided with a stilette should be used. Previously it should be thoroughly cleaned and then sterilized by immersion in absolute alcohol, which is removed just before the operation by immersion in ether. The needle should then be dipped in sterile olive oil to facilitate its passage through the tissues. If the patient is nervous it is well to anaesthetize the area of the puncture by injecting eucaine and adrenalin, or 1-2 c.c. of a 0.5 per cent. solution of novocaine.

The puncture is made almost perpendicularly to the back, with a very slightly inward direction. If the needle does not strike bone after penetrating the skin, it passes on fairly easily for a variable distance till it meets a resistance which is evidently softer than that of bone, and is due to the interlaminal ligament. The feeling imparted to the fingers as the needle passes through this is quite characteristic. The first few drops of fluid should be allowed to flow into a separate test-tube, since this portion may contain some blood. It is well to make the patient rest in bed for a few hours after the operation.

The cerebro-spinal fluid may be tested cytologically, chemically, physico-chemically, and for the Wassermann reaction.

Cytological Examination. This includes an absolute and a differential count of the cells, just as is done in the examination of blood. The enumeration may conveniently be done with a Thoma-Zeiss haemocytometer, mixing nine parts of fluid with one of carbol-thionin, or of a 2 per cent. solution of methyl violet in 4 per cent. glacial acetic acid. The measuring and mixing can be done with an ordinary capillary pipette armed with a rubber teat. This is probably a more accurate method than using one of the special bulb pipettes sold for the purpose, since it is easy in one of the latter for leucocytes to adhere to the side of the bulb and very hard to dislodge them with the little bead in the bulb; at any rate, this is a frequent source of error in ordinary blood leucocyte counts. Three or four total ruled areas should be counted, and the calculation made in the usual way, remembering that the dilution is $\frac{9}{10}$.

A more convenient apparatus than the Thoma-Zeiss is the Fuchs and Rosenthal's counting chamber, in which a larger quantity of fluid (3 c.mm.) can be examined at one time.

Normal cerebro-spinal fluid contains very few cells. The standard instituted by Plaut,¹⁰⁴ which considers any number over 10 per c.mm. as pathological, is usually adopted. In syphilitic and so-called parasymphilitic lesions the greatest and most constant increase is obtained in general paralysis, and next to this comes tabes. In early stages of syphilis Dreyfus¹⁰⁵ has found as many as 750 per c.mm.

The number of cells, though often in accordance with the strength of the Wassermann reaction, is not necessarily parallel, since a high leucocyte count may coincide with a negative Wassermann, and vice versa. The number of cells, though independent of the strength of the Wassermann reaction, is closely parallel to the precipitable substances, globulins, and nucleo-albumins.

The differential count of the cells in cerebro-spinal fluid is effected by centrifugalizing the fluid, spreading a film of the deposit, and, after staining, making the proportional count as when dealing with blood. In syphilis and parasymphilis the cells are exclusively mononuclear—lymphocytes for the most part, with some plasma cells, and perhaps a few large mononuclears with kidney-shaped nuclei. Lymphocytosis is not, however, diagnostic.

Chemical tests. These depend on the precipitation of the protein elements, globulin and nucleo-albumin, by the addition of chemicals. Normal cerebro-spinal fluid contains extremely little protein, so that any amount detected by chemical tests is pathological, though it does not necessarily indicate syphilis. The best known of the chemical tests are the Nonne-Apelt,¹⁰⁶ Ross and Jones,¹⁰⁷ and Noguchi's tests.¹⁰⁸

The Nonne-Apelt consists in the addition to the fluid of an equal quantity of hot saturated solution of ammonium sulphate. About 1 c.c. of the ammonium sulphate, after cooling, is poured into a test-tube, and on it is poured an equal quantity of the cerebro-spinal fluid. In a positive reaction a distinct grey ring forms at the junction of the two fluids. The mixture is then shaken, and if in three minutes it is distinctly opalescent or cloudy, the reaction is positive 'Phase I'.

In the Ross and Jones test 1 c.c. of the fluid is floated on the top of 2 c.c. of saturated ammonium sulphate, and a positive result is indicated by a clear-cut greyish white film at the junction of the two fluids. The ring should be viewed in the dark with a light from the side. The authors say that in their hands the fluid of a general paralytic, diluted eight times, has given the reaction.

In the Noguchi test two parts of fluid are boiled for a few

seconds with five parts of a 10 per cent. dilution of pure butyric acid in physiological salt solution. One part of 4 per cent. sodium hydrate is then added quickly and the mixture boiled again. A positive reaction is indicated by a flocculent precipitate forming in the following two hours.

None of these three chemical tests is diagnostic of syphilis or so-called parasymphilis. A positive result simply indicates an abnormally high protein content, which may be significant in a syphilitic patient showing no other signs.

Physico-chemical test. Lange¹⁰⁹ has evolved a test which he thinks is diagnostic of syphilitic cerebro-spinal changes. A solution of colloid gold is made as follows. To 100 c.c. of double distilled water is added 1 c.c. of 1 per cent. gold chloride solution and 1 c.c. of 2 per cent. potassium hydrate. The mixture is quickly boiled in a Jena glass beaker with energetic shaking, and to it is then added 1 c.c. of 1 per cent. commercial formalin. The result should be a beautiful red-purple transparent fluid without any tinge of blue in it. A 0.4 per cent. solution of pure sodium chloride in double distilled water is also prepared for the purpose of diluting the cerebro-spinal fluid.

A series of dilutions of the cerebro-spinal fluid is made— $\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{40}$, and so on, doubling each time, till a dilution of 1 in about 40,000 is reached in the thirteenth tube. One c.c. of each of these dilutions is placed in a test-tube, and to it is added 5 c.c. of the gold solution ; the addition must be made quickly, not in portions.

The tubes are left at room temperature overnight and then read. The reaction consists in a precipitation of the gold, which is indicated in its various degrees by a change in the colour of the solution from red to reddish-blue, the minimum, blue-red, violet, dark blue, bright blue, light blue, to complete decolorization with a blue precipitate, the maximum reaction. It is in the dilution at which the change in colour reaches its maximum that, according to Lange, lies the distinguishing characteristic of syphilitic fluids. Thus in purulent meningitis the maximum commences at some dilution which is higher than 320, and this applies to normal fluid to which blood has been added. With

syphilitic fluid, on the other hand, the maximum occurs between the dilutions of 1 in 40 and 1 in 80.

The test is therefore qualitative and quantitative : qualitative in the dilution at which the maximum is attained, and quantitative in the grade of the maximum, blue-red to decolorization. The strongest reactions are given by fluids of general paralytics and tabetics, next by cases with very manifest cerebro-spinal syphilis, cases of cranial nerve disturbance, and the weakest by cases of secondary syphilis with nothing more than headache.

If by accident the fluid be contaminated slightly with blood-serum, the syphilis reaction is not necessarily spoiled. The maximum indicating the latter occurs between 40 and 80, and is succeeded by another maximum at or beyond 320, due to the blood-serum. Two results which I obtained will illustrate this point. A sample of cerebro-spinal fluid was drawn from two patients, A and B. A was suffering from syphilitic facial paralysis, and B from secondary syphilis without any cranial sign. In both cases the fluid was drawn off in two portions. In the case of A the first portion appeared quite clear ; in that of B it was obviously contaminated with blood. Both portions were submitted to the test in each case, and the results were as follows :

Case A (facial paralysis). First portion (possibly contaminated with blood) : change of colour commenced at dilution 1 in 10, and reached its maximum at 1 in 40 with complete decolorization and blue precipitate. At 1 in 160 the colour was lilac, but at 1 in 320 decolorization was again almost complete, and the second maximum was reached at 1 in 640. The second portion of fluid showed only one maximum (blue-red at 1 in 40 and nearly as blue at 1 in 80).

Case B. First portion (obviously contaminated with blood) : maximum first reached at 1 in 320 (complete decolorization), with some return of colour at 1 in 2,560. Second portion showed no change in any of the tubes.

It seems from these results that in both cases the first portion was contaminated with blood-serum. Though the reaction could be read in the test of each portion of fluid A, it is possible that

in fluid B the admixture with blood might have interfered with the reading, and it is advisable always to test the second portion drawn off, however clear the first may appear.

In conducting this test it is necessary to ensure that all articles which come into contact with the test fluids should be scrupulously clean, being thoroughly washed with distilled water and then dried by heat.

It is too early yet to pronounce definitely on the clinical value of Lange's test. My own limited experience bears out Lange's claim for it, but, naturally, the fluids from a large number of other pathological conditions of the central nervous system must be examined before the test can be pronounced to be specific.

The Wassermann reaction. It was formerly the custom to test the cerebro-spinal fluid in exactly the same quantity as the blood-serum. Hauptmann and Hössli,¹¹⁰ however, showed the advantage and safety of using relatively larger quantities of fluid than of serum, and this practice is now followed by practically all workers. The result has been to increase the percentage of positive reactions found in tabes, and whereas formerly it was said that in ordinary syphilis of the central nervous system the Wassermann reaction of the cerebro-spinal fluid, as a rule, was negative, it now appears that quite a large proportion of patients in the secondary stage give a positive reaction, especially in syphilitic affections of the cranial nerves and other syphilitic lesions of the central nervous system, apart from tabes and general paralysis.

As the cerebro-spinal fluid contains no complement and has practically no anti-complementary action, it is unnecessary and even undesirable, to heat it.

I have usually carried out the test as follows :

Into each of a series of tubes is put a volume of the fluid in varying dilution, thus :

- 1 volume of undiluted fluid.
- 1 volume of a 1 in 2 dilution.
- 1 volume of a 1 in 4 dilution.
- 1 volume of a 1 in 8 dilution.

Into each of these is put a volume of extract and of complement, respectively, in the same dilutions as in the serum test. Into

another tube (control) is put a volume each of undiluted fluid, complement, and saline. The rest of the procedure is exactly as in the serum test, and the strength of the reaction determined by the number of tubes, excluding the control, in which a positive reaction occurs. As a general rule the cerebro-spinal fluids of cases of general paralysis give the strongest reactions, and then those of tabetics, while the fluids of other cases of syphilis of the central nervous system give reactions only in the tubes containing the larger quantities, undiluted, and 1 in 2 dilutions.

The Wassermann reaction given by the cerebro-spinal fluid in different stages of syphilis. In early primary syphilis a positive reaction has not so far been obtained.

In secondary syphilis Fraenkel¹¹¹ found 5 positive out of 15 cases which showed no symptoms; Bergl and Klausner,¹¹² 4 positive out of 22; and Boas,¹¹³ 1 positive out of 21. In cases showing symptoms of disease of the central nervous system the reaction is almost always positive.

In tertiary syphilis, apart from obvious disease of the central nervous system, the test has been applied very little. Boas tested 8 cases, one with obvious disease of the central nervous system, and all were negative.

In tabes, when the smaller quantity of fluid was used, about 50 per cent. gave a positive reaction, but the use of larger quantities has increased this proportion.

In general paralysis Candler and Mann¹¹⁴ found a positive reaction in 100 per cent. of 109 cases. Morton¹¹⁵ obtained 30 positive out of 30 cases, and Boas¹¹⁶ 189 out of 201. There is an old-standing discussion as to whether the reaction is more often positive in the blood-serum than in the spinal fluid, or vice versa, in tabes and general paralysis. When a smaller quantity of fluid was used than now, it is probable that the reaction was more often positive in the blood-serum, especially in tabes. Now the reverse appears to be the case. Against 100 per cent. positive reactions with the fluid, Candler and Mann found 107 out of 109 positive with the serum. Gilmour¹¹⁷ examined two cases repeatedly, and while the fluid was always positive the serum was negative.

With regard to this question in other syphilitic diseases of the central nervous system, especially in syphilitic meningitis, including syphilitic disturbances of the cerebral nerves, it has frequently been remarked that the blood-serum gave a negative reaction, and this has even been used as an argument against the syphilitic origin of cerebral nerve disturbances after salvarsan injections. But it is easy to understand how the serum may be negative and the fluid positive in such cases. It is well known in other diseases how difficult it is to reach the subarachnoid space with remedies administered through the general circulation, and it follows that specific remedies may destroy the spirochaetes in tissues outside the central nervous system, leaving those within it almost intact. In a case of syphilitic meningitis where the patient (a doctor) had taken mercury fairly regularly by the mouth for some years, I found the serum negative on two examinations at two months' interval, and the spinal fluid was strongly positive each time, with 150 lymphocytes per c.mm. on the second occasion, and a positive Nonne-Apelt reaction.

The Wassermann test of the cerebro-spinal fluid in diagnosis and treatment. A positive reaction indicates syphilis of the central nervous system. The stronger the reaction, the more likely that the case is one of tabes or general paralysis.¹ On the other hand, a negative reaction is strong evidence against general paralysis. As a guide to treatment, the value of the Wassermann and other tests of the cerebro-spinal fluid is being more and more appreciated. Now that it is known how frequently the central nervous system is implicated in early syphilis, slight clinical signs, such as headache, justify a lumbar puncture. If the examination of the fluid then reveals disease of the central nervous system, in view of the difficulty of reaching the lesion through the general circulation, the treatment should be prolonged over a greater length of time than would ordinarily be the case; till, in fact, a further examination shows no further pathological changes.

¹ Fildes and McIntosh (Brain, vol. xxxvi, pt. II) find that in cases of cerebro-spinal syphilis where the cord is affected the reaction is as strong as in parasyphilis, but sensitive to treatment. They attribute the difference between their results in this respect and those of others to their use of heart-cholesterin extract.

APPENDIX

(See page 280)

EXTRACTS NOT GIVEN IN DETAIL IN THE TEXT

NOGUCHI ¹¹⁸

GRIND up liver, heart, or kidney of man, ox, guinea-pig, or dog, with 10 parts of absolute alcohol and keep at 37° C. for several days. Filter and evaporate with the help of a fan. Take up the residue with sufficient ether and allow to stand overnight in a cool place. Decant the clear ethereal solution and evaporate to dryness. Dissolve the residue in a little ether and add ten volumes of acetone. When the precipitate has settled, decant, and allow the remainder of the acetone to evaporate. Preserve the resinous residue in an air-tight jar. For the test dissolve 0.3 gm. in 1 c.c. ether and mix the ethereal solution with 9 c.c. of methyl alcohol. From this make the emulsion as required by adding 1 c.c. to 9 c.c. of saline.

The antigen is tested for haemolytic properties by adding 0.4 c.c. of the emulsion to 1 c.c. of a 1 per cent. corpuscle suspension and incubating for 2 hours. Its anti-complementary power is tested by mixing 0.4 c.c. of the emulsion with 0.1 c.c. of 1 in 2.5 complement, 0.9 c.c. saline, and 0.1 c.c. of a 10 per cent. suspension of cells, incubating for 1 hour, adding haemolytic amboceptor, and incubating for 2 hours.

The antigenic power is estimated by incubating falling amounts of emulsion with syphilitic serum and complement. The smallest amount of emulsion which causes complete inhibition of lysis is the antigen dose. A suitable antigen has an antigen dose which is $\frac{1}{20}$ the anti-complementary, being generally 0.02 c.c., and five doses (0.1 c.c.) are usually used in the test.

CANDLER AND MANN ¹¹⁹

Weighed syphilitic liver is ground up with silver sand and plaster of Paris and the powdered residue is washed with acetone to remove haemolytic and anti-complementary bodies. The acetone is poured away and the residue allowed to dry at room temperature and transferred to a flask. Sufficient alcohol is added to make 4 c.c. to every gramme of original liver and the mixture left at room temperature for two to three days before filtering.

It is stored in the refrigerator in dark bottles. (Quite probably normal solid organ could be used instead of syphilitic liver.)

BROWNING, CRUICKSHANK AND MACKENZIE'S LECITHIN-CHOLESTERIN * 120

The lecithin is extracted from ox-liver in the following manner. A crude extract of ox-liver is made by digesting it with four parts of 95 per cent. alcohol for three or four days at room temperature, the mixture being stirred at least once a day. After filtering, the extract is evaporated to a syrupy mass in a flat porcelain dish on a water-bath at 60° C.

The syrupy mass is rubbed up with quartz sand (about 50 gm. of sand to 1,000 c.c. of original extract). A firm mass results, which is placed in a spherical flask closed with a rubber bung through which passes a piece of quill tubing drawn to a capillary point at the end.

Ethyl acetate is placed in the flask, which is then stoppered and immersed up to the neck in a water-bath at 60° C. The flask is shaken repeatedly, and after ten minutes the ethyl acetate is filtered through fat-free paper in a hot-water funnel, the water in the funnel being kept at 60° C. More ethyl acetate is added to the residue in the flask and the process repeated. The residue is extracted with ethyl acetate a third time, a total of about 170 c.c. ethyl acetate being required to extract the residue of 1,000 c.c. crude extract.

The ethyl acetate solution is placed in the refrigerator overnight and a precipitate falls out. The precipitate is taken and again dissolved in ethyl acetate at 60° C. and the solution put in the ice-chest another night.

The precipitate is dissolved in ether and the solution placed in a cylinder with four times its volume of acetone, which causes a precipitate. The mixture is shaken for some minutes to assist precipitation. After ten minutes the clear supernatant fluid is poured off and the precipitate dissolved again in ether. The precipitation with acetone is repeated twice.

The last precipitate is rubbed up with sand and extracted with pure ethyl alcohol (100 c.c. to the precipitate from 1,000 c.c. of original extract) at room temperature for twenty-four hours.

This makes the solution of lecithin. Its strength is estimated by taking from 5 to 10 c.c., evaporating at 57° C. to dryness and weighing the residue. It is made to a strength of 0.75 per cent.

Lecithin-cholesterin solution. To some of the 0.75 per cent. solution of lecithin is added cholesterin (Kahlbaum or Poulenc Frères) in excess, 1 to 1.2 gm. to 100 c.c. of lecithin solution, and the mixture is shaken repeatedly. It is ready for use in about a week, but if required earlier solution of the cholesterin is assisted by brief and gentle warming on a water-bath.

* Sold by Messrs. Thomson, Skinner and Hamilton, 38 Sauchiehall Street, Glasgow.

This lecithin-cholesterin solution makes an excellent artificial extract for the ordinary original test (see p. 258).

KOLLE AND STINER ¹²¹

Rub up 1 gm. dried organ (syphilitic liver, normal heart, &c.) in a mortar with pure acetone 20-50 c.c.

Place for 8-10 hours in the incubator, for the same time in the ice-chest, and leave for a day at room temperature. Filter and store in amber bottle with rubber bung.

F. LESSER ¹²²

Extract ground-up heart-muscle with ether. Evaporate the ether and extract the residue with water. The result is a milky emulsion.

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